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## Title

Regression in Autism Spectrum Disorder: A Critical Overview of Retrospective Findings and Recommendations for Future Research (in press, March 2019).

Invited Contribution to the Special Issue of *Neuroscience and Biobehavioral Reviews* on “Regression in Developmental Disorders”

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## Abstract

Historically, two onset patterns in autism spectrum disorder (ASD) were described: an early onset of symptoms and a regression in which one-third appear to show a loss of previously established skills in the second year of life. Since this phenomenon could represent a distinct ASD subtype and provide more insight into the etiology, diagnosis and prognosis, many studies have compared these two groups. The present review discusses definitions, etiology and methods used in research with a retrospective design and provides an overview of the results on early development and outcomes. However, retrospective research has not provided clear answers on regression as a distinct subtype of ASD and the historic division between early onset and regression does not seem to fit the empirical findings. Based on inconsistent results, future research on onset patterns in ASD needs to be more systematic on the definitions and methods used. Several recommendations to enhance the reliability of future retrospective results are discussed. The combination of a categorical and dimensional approach provides a new interesting framework.

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## **Main Text**

### **Introduction**

Autism spectrum disorder (ASD) is a neurodevelopmental condition characterized by social communication and interaction difficulties and the presence of restricted and repetitive patterns of behavior, interests and activities and sensory processing anomalies causing functional impairment in social, educational, and occupational domains [American Psychiatric Association (APA), 2013; Bölte et al., 2018; World Health Organization (WHO), 2018]. Historically, literature suggests that the behavioral signs of ASD emerge through two major distinct patterns of development: an early onset in the first year of life and a regressive onset, later in the second year. The early onset pattern is defined by atypicalities in speech-language and socio-communicative development (e.g., productive and receptive language forms and functions, turn taking, joint attention, affect sharing and imitation) in the first 12 months and is suggested to occur in the majority of individuals with ASD (Lord,

Shulman, & DiLavore, 2004; Ozonoff, Heung, Byrd, Hansen, & Hertz-Picciotto, 2008). However, some children later identified with ASD initially show a period of apparently typical development followed by a considerable loss of previously established skills somewhere in the second year of life, a phenomenon termed “regression” (Barger, Campbell, & McDonough, 2013; Pearson, Charman, Happé, Bolton, & McEwen, 2018), which will be the focus of the present review.

Regression was first described over 110 years ago by Theodor Heller (Heller, 1908). Heller wrote about a condition he termed ‘Dementia Infantilis’ in which children suddenly lost adaptive functions such as sociability and language skills and developed stereotyped behaviors after a mostly normal development until their third or fourth year of life with no clear cause such as acute illness, convulsions, or trauma (Heller, 1908; Westphal, Schelinski, Volkmar, & Pelphrey, 2013). Later on, regression in autism was reported in one of the 11 children described by Kanner in his seminal paper “Autistic Disturbances of Affective Contact” (Kanner, 1943). In a later publication, Kanner and Leon Eisenberg described a number of children who were reported to develop typically in the first 18 to 20 months of life and showed a symptom onset after language regression in combination with withdrawal of affect and failure to progress socially (Kanner & Eisenberg, 1956). In the same year, Eisenberg conducted one of the first follow-up studies with 63 children with autism and described several children with language loss who had a poor later prognosis (Eisenberg, 1956). Further, in the 1960s and 1980s additional studies reporting on regression in infants with autism were published (Hoshino et al., 1987; Kurita, 1985; Lotter, 1966; Wolff & Chess, 1964). Since then, the phenomenon of regression has been discussed in the ASD literature for several decades. Some researchers suggested that it could represent a distinct ASD subtype which provides insight into the etiology of ASD, has an important diagnostic use and bears prognostic value or relates to later outcomes (Rutter, 2006; Stefanatos, 2008; Williams, Brignell, Prior, Bartak, & Roberts, 2015). Today, the interest in the etiological and diagnostic utility, and clinical significance of regression in ASD continues (Barger, Campbell, & Simmons, 2017; Pearson et al., 2018; Thurm, Powell, Neul, Wagner, & Zwaigenbaum, 2018).

Because of mixed results in the regression literature, doubt has risen about the adequacy of a dichotomous distinction of onset patterns in ASD. Some researchers (e.g., Lord et al., 2004; Ozonoff, Heung, et al., 2008) argued that a simple division between regressive (ASD+REG) and non-regressive ASD (ASD-REG) does not fit the empirical data well. Hence, an additional mixed “early onset + regression” pattern, defined by the presence of early characteristics of ASD or developmental delays followed by a loss of skills was proposed (Lord et al., 2004; Ozonoff et al., 2011; Ozonoff, Heung, et al., 2008). Additionally, also a “plateau” or “stagnation” pattern characterized by intact early social development and/or non-specific atypicalities followed by a failure to progress and gain new skills, has been suggested (Kalb, Law, Landa, & Law, 2010; Ozonoff et al., 2011; Shumway et al., 2011; Siperstein & Volkmar, 2004). Another suggestion is to consider the emergence of ASD characteristics as a continuum with early onset and regression at the extremes so that variable combinations and timings of these processes can lead to symptom onset at a certain point in development (Ozonoff et al., 2008). Other researchers argue that developmental trajectories of children diagnosed with ASD are as individualized as those of typically developing children. They suggest that regression in ASD may best be represented as a dimensional phenomenon that starts with a continuum of varying degrees of early delays in the attainment of socio-communicative skills and then may be followed by a continuum of varying degrees of loss (Thurm et al., 2014). The one end of the regression continuum could represent children who show already very early a minimal loss of social interest so that the regression is difficult to measure or detect by parents (Ozonoff et al., 2011). The other end may represent children who experience late, rapid and dramatic losses of social interest and communication skills which can be more easily detected (Ozonoff et al., 2011). These theoretical insights are in line with some earlier studies (e.g., Davidovitch, Glick, Holtzman, Tirosh, & Safir, 2000; Werner, Dawson, Munson, & Osterling, 2005) in which the age of onset of ASD characteristics and the occurrence of loss of skills were recognized as two separate aspects of the early development in ASD. In this respect, the presence of regression does not necessarily imply a late onset of ASD characteristics because some children with regression show an early atypical development (Werner

et al., 2005). Characteristics of the early development before regression are discussed in the section below.

Over the last two decades, several reviews have described the phenomenon of regression with a main focus on the prevalence, onset, and types of skills that are lost (e.g., Barger et al., 2013; Holland & Brown, 2017; Matson & Kozlowski, 2010; Ozonoff et al., 2008; Rogers, 2004; Stefanatos, 2008; Williams et al., 2015). Concerning the etiology of regression, there has been a sizeable number of studies on the relationship with epilepsy which were recently reviewed by Barger, Campbell and Simmons (2017). However, none of the reviews so far has comprehensively addressed findings and insights on early development before regression and later development following regression. First, we are highlighting the present considerations on the definition, prevalence and etiology of regression, and their role within ASD diagnosis. Further, retrospective methods used to measure regression are discussed and evaluated. Next, we will provide an overview and discussion of the findings in the literature using a retrospective design concerning early development before and development after regression in children with ASD. Findings from prospective family risk sibling studies are still preliminary and mainly focus on prevalence, onset and types of loss of skills. Because these studies have been reviewed elsewhere (see Pearson et al., 2018 and Ozonoff & Iosif, this issue) their conclusions are only briefly discussed in the light of an integration with retrospective results. Lastly, we aim to provide an overview of the present challenges and perspectives on research on regression in ASD and set out several recommendations for future studies.

## **Definition of Regression: Prevalence, Onset, and Etiology**

In most studies, regression is described as a period of apparently typical development for the first one or two years of life, followed by an abrupt or gradual loss of previously acquired skills with or without recovery (Barger et al., 2013; Lainhart et al., 2002; Williams et al., 2015). However, after more than 70 years of research on this phenomenon, there is still no published, standardized definition of how ‘regression’ specifically should be described. Moreover, a substantial number of

studies on regression did not provide an operational definition of regression (Barger et al., 2013). Because regression was often defined as loss of productive language without including loss of other non-language skills and/or information on development before regression or the presence of a stagnation, prior research may not have fully captured regression and/or other specific onset patterns, mainly leading to a significant underestimation of the prevalence of regression (Hansen et al., 2008; Ozonoff, Heung, et al., 2008). Therefore, it is also very difficult to summarize results on regression rates, onset, domains, etiology, early development and outcomes that are broadly varying and depend on the specificity and inclusiveness of the definition of regression, the sampling methods and the methodology (e.g., retrospective or prospective approaches) used.

With regard to the definition of regression, there is wide variability in the types of skills that are lost. Some researchers, from mostly early studies on regression, argue that loss of language skills is central to regression in ASD (e.g., Brown & Prelock, 1995; Jones & Campbell, 2010; Kurita, 1985). One reason that language skills have most typically been reported is that it is more unconcealed and clearly recognizable for the parents than non-verbal communication and social interaction skills. As a consequence, in some studies (e.g., Kurita, 1985; Lainhart et al., 2002), children who only experienced social skill losses without regression in language were included in the non-regression group. More recently, researchers have also included regression in other domains than spoken language within the definition, including loss of non-verbal communication (e.g., gestures), more basic social skills (e.g., the use of eye gaze), social withdrawal, and/or loss in play, motor, and adaptive skills (e.g., Davidovitch, Glick, Holtzman, Tirosh, & Safir, 2000; Gadow, Perlman, & Weber, 2017; Goin-Kochel, Esler, Kanne, & Hus, 2014; Hansen et al., 2008; Ozonoff et al., 2005; Siperstein & Volkmar, 2004).

Further, it is also important to distinguish a loss of skills from a stagnation of skills or “plateau” since in some children a loss of skills could be simply a failure to progress their acquired skills to a more developmentally advanced level (Hansen et al., 2008; Ozonoff, Heung, et al., 2008; Siperstein & Volkmar, 2004). It is possible that in many of the studies on regression, children with a plateau

pattern in language development, social and other skills were wrongly included in the early onset or regression group. Up to now, six articles distinguished the plateau pattern from regression with rates ranging from 8 to 23.1% (mean plateau rate: 14.1%; Jones & Campbell, 2010; Kalb et al., 2010; Ozonoff et al., 2011; Shumway et al., 2011; Siperstein & Volkmar, 2004; Wiggins, Rice, & Baio, 2009). In total, 581 children with a plateau pattern have been described of whom 469 are included in the online research survey article of Kalb et al. (2010). Since the group of children classified as showing a plateau pattern was relatively small in most of these studies, these children were added to the non-regression group to analyze group differences. **Notably, in a study by Wiggins et al. (2009) it was concluded that regression and plateau were more likely to co-occur than to exist separately, since of the 22 children who did not progress in skill development, 16 were also noticed to lose skills around the age of 24 and 25 months respectively.**

A review which included a meta-analysis of 85 studies (total sample size = 29,035) on regression in ASD revealed an overall prevalence of 32.1% (95% CI: 29.5-34.8; Barger et al., 2013). However, the prevalence rate of regression was subject to the sampling approach used: population-based (21.8%), clinic-based (33.6%) and parent survey-based (40.8%; Barger et al., 2013). Since population-based studies aim to include a representative sample and are more typically focused on measuring the prevalence, these studies may provide the most accurate indicator of the regression rate (Barger et al., 2013). Although some studies suggested an inverse relationship between sample size of the study and regression prevalence (e.g., Rogers, 2004), no such evidence was found in the meta-analysis by Barger and colleagues (2013). Regression prevalence rates also differed according to four types of regression: language regression (24.9%); language/social regression (38.1%); mixed or other domains of regression such as loss of adaptive skills (32.5%); and unspecified regression when no operational definition of regression was provided (39.1%; Barger et al., 2013). Hence, it seems that regression most often occurs in language (defined as loss of words, reduction of syntactic complexity, or loss or pre-linguistic verbal abilities such as babbling) – which is also more easy for parents to detect – and/or social skills (defined as loss of social interaction skills such as social smiling or joint attention;



Barger et al., 2013). However, only a few studies clearly disentangled social regression from other types of regression (Barger et al., 2013; Hansen et al., 2008; Ozonoff et al., 2010). In most retrospective studies using a clear distinction between losses in language capacities and social skills, it was found that it is common for children with loss of verbal forms and functions to also lose skills in social development (e.g., response to name and eye contact; Goldberg et al., 2003; Lord et al., 2004; Ozonoff, Williams, & Landa, 2005; Zhang et al., 2018). On the other hand, since most children who lose skills of social interest and engagement have not yet acquired language at the time of regression, a substantial amount of children only show regression in social development (Goldberg et al., 2003; Hansen et al., 2008; Kurita, 1985; Ozonoff et al., 2005). Additionally, very few differences between children who lose both skills in language and social domains and those who only lose social skills have been found (Lord et al., 2004; Luyster et al., 2005). Further, it seems also more difficult to get information on the prevalence and onset age of loss of language skills because most researchers only investigated loss of single words or multi-word utterances. Thus, children who regressed in earlier language stages such as pre-linguistic vocalizations, babbling, or proto-word production were not included in the language regression group.

Concerning the age of onset, regression was found to start at a mean age of 1.78 years (95% CI: 1.67-1.89) or 21.4 months (Barger et al., 2013). However, given that most studies on regression used parent report, it is difficult to distinguish the mean onset age from the age of parental recognition (Goldberg et al., 2003). Probably due to a recall bias called ‘forward telescoping’ (see also the section below on “Retrospective Methods in Research on Regression”), later age of onset was predicted by older age of the child at evaluation (Barger et al., 2013). In addition, some researchers argue that the onset of regression may depend on the stage of brain maturation and developmental level of the child rather than chronological age (Lord et al., 2004; Pickles et al., 2009). Further, different developmental domains seem to be associated with different ages of onset. Some researchers reported an earlier onset age of non-language regression compared to language regression. For example, a retrospective study by Goldberg et al. (2003), in which parent reports of regression were

validated by home-video analyses, found an average onset age of 18 months for non-language regression versus 21 months for language regression. While sometimes regression seems to occur very suddenly it sets in more gradually in 60% to 70% of children (e.g., over a 3-month period of time; Matson, Wilkins, & Fodstad, 2010), which could have an impact on both the prevalence of regression and identification of the onset age (Goldberg et al., 2003; Ozonoff, Williams, & Landa, 2005). In a study by Thurm et al. (2014), it was found that loss of specific socio-communication and speech-language skills was reported by parents to begin at a wide range of ages, from 9 to 36 months.

It is important to note that most of the above-described findings are based on retrospective parent report and home video-analyses. Up until now, only a limited number of prospective longitudinal studies reported some preliminary findings on the prevalence, onset and types of regression in siblings with an older brother or sister with ASD (often referred to as 'high-risk' siblings or HR-sibs; see Pearson et al., 2018 and Ozonoff & Iosif, this issue), who receive the diagnosis of ASD later on. Based on retrospective results, the regression pattern is suggested to be a separate phenotype of ASD and to only occur in a subgroup of children with ASD (i.e. 32.1%) at a mean age of 21.4 months (Barger et al., 2013). Similarly, some of the prospective studies suggest that a definite loss of language skills as measured by the Mullen Scales of Early Learning (MSEL; Mullen, 1995) occurs in 17 to 42% (Landa & Garrett-Mayer, 2006) or 19 to 29% (Landa, Gross, Stuart, & Faherty, 2013) of high risk infants with a later diagnosis of ASD. However, it is important to mention that some of the prospective longitudinal studies (e.g., Landa et al., 2013) only included standardized scores or group data which makes it more difficult to differentiate a failure to progress from actual skill loss (see also the section below on "A Shift Towards Prospective, Longitudinal Research on Onset Patterns in ASD" and Pearson et al., 2018). Moreover, prospective studies that conduct a very detailed analysis of social communication behavior and social engagement skills in minute-by-minute segments through coding, seem able to detect earlier (between 6 and 18 months) and more gradual, subtle declines or regression in the majority (up to 88%) of infant siblings with ASD (Bryson et al.,

2007; Landa, Holman, & Garrett-Mayer, 2007; Lord, Luyster, Guthrie, & Pickles, 2012; Ozonoff et al., 2010, 2018). These declining trajectories may be less easily captured in real-time observation by parents or by standardized instruments (such as the MSEL). Based on these prospective results, it is suggested that regression may occur in almost all children with ASD (Ozonoff et al., 2010; 2018; Pickles et al., 2009; Thurm et al., 2014) and would therefore be the natural course of onset of ASD, as was also implied in prior retrospective research (e.g., Davidovitch et al., 2000).

To date, similar to ASD in general, the precise origins of regression are still largely unknown but probably linked to a complex interaction between biological and environmental factors (Barger et al., 2013, 2017; Sven Bölte, Girdler, & Marschik, 2018; Thurm et al., 2018). Based on the heterogeneity of regression in ASD, it seems likely that multiple possible etiological mechanisms can lead to regression as a final common pathway (Stefanatos, 2008). At this point, we do not know if regression in ASD can be conceptualized on a continuum or if there are separate underlying processes in loss of skills at younger and later ages. Hence, it may be important to understand regression in ASD from a neurological or biobehavioral perspective. Other disorders that are also characterized by regression and of which the underlying biology is known better, such as mitochondrial diseases, Rett syndrome (which was for a long time part of the “spectrum”; Marschik et al., 2013; Neul et al., 2010; for details on regression in Rett syndrome see Einspieler & Marschik, this issue) and **epileptic encephalopathy** (e.g., Landau-Kleffner syndrome) could provide a context through which questions about underlying mechanisms of regression in ASD could be explored. Recently, the over-pruning hypothesis of ASD as a neural network modelling approach to explain the underlying neurobiology of regression was introduced, proposing that regression would be caused by an over-aggressive pruning of strong connections generating loss of skills (Thomas, Davis, Karmiloff-Smith, Knowland, & Charman, 2016; Thomas, Knowland, & Karmiloff-Smith, 2011). Based on a workshop from the US National Institute of Mental Health (NIMH), Thurm et al. (2018) provided an extensive overview of possible neurobiological mechanisms of regression and suggestions for the use of model systems such as the pathogenic mechanisms that underlie regression in Rett syndrome. Further, cutting-edge methods,

including non-invasive imaging which could afford opportunities for a better understanding of the neurobiological pathways that result in regression, were proposed (Thurm et al., 2018).

With regard to the literature on the etiology of regression in ASD, it is clear that most studies until now have been based on relatively small samples, retrospective parent reports and cross-sectional associations. Moreover, considering the inconsistencies in the definition of regression, results should be interpreted with caution and additional, especially prospective, research is needed to confirm these preliminary findings.

Environmental mechanisms which could be related to regression include psychosocial stressors (Kobayashi & Murata, 1998; Lainhart et al., 2002), prenatal and obstetric (post-natal) complications and viral infections (Christopher, Sears, Williams, Oliver, & Hersh, 2004; Davidovitch et al., 2000; Hansen et al., 2008; Kurita, 1985; Wilson et al., 2003) and socio-economic status or ethnicity (Christopher et al., 2004; Hansen et al., 2008; Rogers, 2004). Further, no associations between regression and the measles-mumps-rubella (MMR) vaccination (Baird et al., 2008; Richler et al., 2006) were found. Some authors suggest that in children with regression a biological event alters brain development during critical time windows and evokes the onset of seizures or abnormal EEG activity (Baird, Robinson, Boyd, & Charman, 2006; Oslejsková et al., 2008; Tuchman & Rapin, 1997). However, a recent meta-analysis of Barger et al. (2017) indicated a relatively weak relationship between regression and epilepsy or atypical epileptiform electroencephalograms (aeEEG). Results were difficult to interpret because different methods and definitions to measure and describe epilepsy were used and only small effect sizes have been reported (Barger et al., 2017). Based on neuroimaging findings, regression has also been associated with abnormal brain enlargement (Nordahl et al., 2011; Valvo et al., 2015). Further, mitochondrial dysfunctions are increasingly being considered as possibly related to ASD (Haas, 2010; Rossignol & Frye, 2012). The meta-analysis of Rossignol and Frye (2012) concluded that regression in language, social interaction, play and motor skills was noted in 52% of the children with ASD who had comorbid mitochondrial disease or abnormal biochemical markers of mitochondrial function. This figure is much higher than in the

general population of ASD (i.e., 32.1%; Barger et al., 2013) and could imply that mitochondrial dysfunctions contributed to regression in the cases with ASD and comorbid mitochondrial disease. Evidence for this assumption is provided by the finding that mitochondrial dysfunction can cause reduced synaptic neurotransmitter release in for example the inhibitory GABAergic interneurons (Anderson, Hooker, & Herbert, 2008). These interneurons have an important role in brain development between 12 and 30 months (Herlenius & Lagercrantz, 2004), which is also the age range when regression in ASD is most commonly reported (Barger et al., 2013; Rossignol & Frye, 2012). Moreover, mitochondrial dysfunction could also lead to immune abnormalities seen in individuals with ASD and alternatively, an autoimmune process can also drive mitochondrial dysfunction through an inflammatory process resulting in developmental regression after a period of typical development (Rose et al., 2018; Shoffner et al., 2010). This also corresponds with emerging findings suggesting that in some cases of ASD+REG an immune dysregulation may be involved (Duffy et al., 2014; Hacoen et al., 2016; Molloy et al., 2006; Scott, Shi, Andriashek, Clark, & Goez, 2017; Wasilewska, Kaczmarek, Stasiak-Barmuta, Tobolczyk, & Kowalewska, 2012).

Lastly, some researchers proposed that regression in ASD may occur in a particular genetic subgroup (Gregg et al., 2008; Molloy, Keddache, & Martin, 2005), but their findings could not be replicated (Parr, Lamb, Bailey, & Monaco, 2006). On the other hand, in a study by Philippe et al. (2015) a link was found between a partial deletion of the SHANK3 gene – which plays a role in the Phelan-McDermid syndrome, also characterized by regression (De Rubeis et al., 2018) – and regression in social and communicative skills with onset around the age of 3 years. Further, Goin-Kochel, Trinh, Barber, and Bernier (2017) examined rates of parent-reported regression with likely gene disrupting mutations from five distinct classes and found that children with ASD and mutations in postsynaptic density genes were more likely to have a regression. Additional evidence for a possible role of de novo genetic mutations in regression can be found in an exploratory study by Gupta et al. (2017) in which a certain expression profile of candidate genes for Childhood Disintegrative Disorder (CDD; also known as Heller's syndrome (Heller, 1908)) was similar to that of an independent cohort of

simplex ASD probands with regression, but not that of ASD probands without regression. In the previous edition of the DSM (DSM-IV-TR; APA, 2000) the condition of CDD was defined separately as typical development in at least the first two years after birth followed by a rapid loss of skills before the age of 10. Dramatic skill losses are present not only in the language and social-communication domain but also in other areas such as play, motor and adaptive skills, and bowel or bladder control together with the occurrence of anxiety behavior and leading to significant intellectual disability (Stefanatos, 2008). However, the condition of CDD was found to be very rare (pooled estimation of 1.7 per 100,000; Fombonne, 2002) and there is only a limited amount of research on CDD in which no common etiological factor could be identified. Because of the lack of evidence to justify the distinction between ASD and CDD, in the DSM-5 (APA, 2013), CDD is no longer a separate disorder but is included within the diagnosis of ASD.

### **The Role of Regression in ASD**

Although the formal diagnostic criteria for ASD in DSM-5 (APA, 2013) do not include regression, it can be added as a clinical specifier to the diagnosis of ASD. Several researchers suggest that regression is fairly specific to ASD and could thus be an important diagnostic indicator (Lord et al., 2004; Luyster et al., 2005). Therefore, in several studies, the prevalence of reported language regression in ASD was compared to the prevalence of this form of regression in other conditions such as specific language impairment (1% in Pickles et al., 2009) and developmental delay (3% in Baird et al., 2008 and 14% in Lord et al., 2004). Generally, loss in more heterogeneous skills or less specific loss of imitated words or non-word vocalizations seemed to occur at a similar rate in children with ASD as well as children with developmental delays and typically developing children (Lord et al., 2004). In the Thurm et al. (2014) study, which measured both verbal and non-verbal skills, 24% of the developmental delay group was reported to have lost skills. Among children with typical development, loss of skills was rare with only one child reported to have lost language skills such as the use of first words (Thurm et al., 2014). In prospective research, trajectories including loss of skills

in both language and socio-communicative skills were found in a substantial amount of children with specific language impairments and typical development (e.g., Brignell et al., 2017; Landa, Gross, Stuart, & Faherty, 2013). Even though regressions are reported in children with language impairments and typical development, these do seem like they are qualitatively different and not permanent, reflecting 'natural' ups and downs rather than a clear loss of skills, which is seen in children with ASD. However, more research on loss of skills in typically developing children has to be conducted and future studies on regression on ASD could benefit from including control groups of children with a typical or delayed development without ASD.

## **Retrospective Methods in Research on Regression**

Currently, there is no golden standard retrospective method to measure the occurrence, onset, and other characteristics of developmental regression in children with ASD. Traditionally, retrospective parent report and analysis of family videos, recorded prior to diagnosis, are the commonly used methods by researchers to explore the emergence of characteristics in ASD (reviewed by Yirmiya & Charman, 2010 and see also Bölte et al., 2016). Based on recall reliability problems and the use of arbitrary cut-offs and other restrictions within the interviews and questionnaires, it is clear that parent report may result in an underestimation of the regression prevalence in ASD. Hence, it is likely that some children were incorrectly classified in the non-regression groups. Although both parent report and home-video analysis are accompanied by limitations concerning reliability, representativeness, and generalizability, several improvements such as the combination of more detailed interviews (e.g., Thurm et al., 2014) and questionnaires (e.g., Ozonoff et al., 2005), the use of strategies to enhance memories during parent report and validation by home-video analysis (e.g., Werner & Dawson, 2005) resulted in more reliable findings on the characteristics of regression in ASD.

### **Retrospective Parent Report**

Most research on regression in ASD is based on retrospective parent report in which researchers ask parents, mostly during initial diagnostic assessment, if their child ever lost skills in a certain domain during development. Since parent report is an efficient, informative and cost-effective method to collect information on the early development of the child, it is commonly used in both research and clinical practice. However, there is a broad variation in the instruments that are used. The following overview contains an evaluation of several interviews and questionnaires that are most commonly used and validated in retrospective research on regression.

The *Autism Diagnostic Interview-Revised* (ADI-R; Rutter et al., 2008) is the most widely used instrument to measure the attainment and loss of skills in the ASD context. It contains a section of questions to collect detailed information about skills that are lost, onset age, duration, and potential factors associated with the loss. Considering language regression, the ADI-R requires a communicative use of at least five different words on a daily basis for at least 3 months prior to the reported loss and that there has been a loss of the skill for at least 3 months (Rutter et al., 2008). If parental report does not meet these criteria (e.g., fewer words were used or they were only used for less than 3 months, or parents reported a loss of pre-conversational speech such as loss of babbling or gesture use), the ADI-R criteria for language regression will not be met and these children would not be included in the regression group in most studies. Although several studies included sub-threshold loss groups (e.g., Goin-Kochel et al., 2014) to deal with these kinds of losses, there is still no consensus on how these sub-threshold losses that are not conform to ADI-R definitions should be specifically defined (Ozonoff et al., 2008). Further, also potential losses in other skills such as motor, self-help, play, and social abilities are examined. However, these questions are open-ended and less specific which makes it difficult for parents to report for example subtle social-communication losses, leading to an underestimation of regression in other skills than language. Since the ADI-R does not include detailed and follow-up questions about the nature and course of regression in non-language domains (Goldberg, Thorsen, Osann, & Spence, 2008), several researchers developed an additional structured caregiver interview. The parent-reported *Regression Validation Interview* (RVI) was



created by Lord et al. (2004) and also used by Luyster et al. (2005), Richler et al. (2006) and more recently by Thurm et al. (2014; *Regression Supplemental Questions* (RSQ)). The interview collects information on the child's acquisition of major milestones in communication skills and word loss (through questions adapted from the ADI-R) and on productive and receptive language skills (through questions adapted from the MacArthur-Bates Communicative Development Inventory: Words and Gestures Form or CDI; Fenson, 1989). For each skill, the parent was asked if their child had acquired the skill prior to the age of 24 months, and if so, whether the child had ever become worse or lost the skill for at least 1 month prior to the age of 36 months. Another supplemental interview for the ADI-R, the *Regression Supplement Form* (RSF; Goldberg et al., 2003) was used to probe for type of loss, timing of loss and possible regain of 18 specific skills which represent the domains of spoken language, non-verbal communication, social interest and responsiveness, and play and imagination. The RSF has been shown to have good inter-coder reliability with observer-coded home videotapes (91%) and validity (Goldberg et al., 2003). *In the study by Goin-Kochel et al. (2014) a Loss Supplement Questionnaire was used which includes new queries about both 'full' (3 months) and 'subthreshold' (1 month) losses in cooing, balling, and curiosity or alertness and their onset age and duration.*

The *Early Development Questionnaire* (EDQ; Ozonoff et al., 2005) is a parent questionnaire which collects retrospective information about the onset of ASD characteristics and other aspects of early development. The questionnaire contains items about early social and communicative deficits and stereotyped behaviors before 18 months or up to the start of the regression, on the age of attainment of particular developmental milestones and the loss of communication, social, adaptive and motor skills (including onset, course and potential causes). Another questionnaire used in research on regression in ASD is *The Parent Questionnaire* developed by Gadow, DeVincent and Schneider (2008). Concerning regression, this questionnaire asks if there was a period during which the child seemed to lose earlier acquired communication, social interaction and responsiveness, play and imagination, academic or vocational, motor and toileting skills, other than during a physical illness (Gadow et al., 2017).

Further, several studies were primarily relying on information on regression written into the child's earlier educational or clinical/medical records (e.g., Bradley, Boan, Cohen, Charles, & Carpenter, 2016; Wiggins, Rice, & Baio, 2009). A strength of this method is that the use of record-review data controls for parental reporting bias and use of small, clinical samples by uniformly gathering and recording data on a population-based cohort of children (Wiggins et al., 2009). Conversely, an important limitation is that the information obtained through these records does not always provide a complete picture of a child's development and it is still a kind of 'secondary source', without any information on the verification of the actual occurrence of regression.

Although parent report is still the most practical or user-friendly, clinically usable and cost-effective method to explore the emergence of ASD characteristics, there are several limitations. First, there are several complications concerning memory and interpretation that compromise its value. Various factors influence parents' ability to accurately recall the details of their children's early development such as the presence of older siblings with ASD (Dawson, 2011; De Giacomo & Fombonne, 1998). Further, parents' memories might be influenced by the knowledge of their child's eventual diagnosis, which is a form of confirmation bias (Ozonoff et al., 2008). Another form of recall bias is "forward telescoping" (Janssen, Chessa, & Murre, 2006; Loftus & Marburger, 1983) in which people report an event as having occurred more recently than it actually took place. When parents are asked about the developmental history of their child, the achievement of milestones such as first words are often reported at a later age than they actually were and the age at acquisition of a milestone can become later and later as the child grows older which makes it more likely for the skill to be classified as 'delayed' (e.g., Hus, Taylor, & Lord, 2011). Regarding reports of symptom onset, parents of older children seem to report later ages of regression onset (Barger et al., 2013; Lord et al., 2004) and Tuchman and Rapin (1997) found that parents of younger children are more likely to report regression compared to parents of older children. In a recent prospective longitudinal study by Ozonoff, Li, Deprey, Hanzel, & Iosif (2018) change in onset classification was associated with parents not recalling a regression at the second visit that they had reported when interviewed earlier

1 at the first visit. In a study by Jones et al. (2015) it was also found that timing of consecutive  
2 interview questions impacts responses of caregivers, namely, when information on history of  
3 symptoms was asked first, less severe past and current behavior was reported compared to  
4 caregivers reporting current and history of symptoms together. Based on these biases and the fact  
5 that developmental histories are often collected years after a loss of skills has occurred, it may be  
6 rather difficult to obtain detailed and accurate information concerning the child's development  
7 immediately prior to the regression and the timing of earlier events (Stefanatos, 2008). Second,  
8 parents' knowledge of developmental stages in children could significantly differ causing a lack of  
9 sensitivity to atypicalities in the development of their child (Ozonoff et al., 2008). For some parents it  
10 is also difficult to admit that the development of their child is atypical and initially deny that there  
11 are problems (Dawson, 2011). It is possible that parents may not seek immediate professional help  
12 when the regression occurs unless the regression was very abrupt or associated with medical  
13 symptoms such as seizures (Davidovitch et al., 2000). Some parents may also connect the  
14 manifestation of regression to minor illnesses, traumatic events or other stressors in the  
15 environment, or even the widely recognized difficult developmental period the "terrible two's"  
16 (Stefanatos, 2008). Third, parent reports on regression also depend on the types of questions that  
17 are asked in both interviews and questionnaires such as the focus on language versus social-  
18 communication skill loss (Dawson, 2011) or the distinction between loss and stagnation of skills.

19 Since the interviewer can further examine if parents are truly reporting a loss of skills that  
20 conforms with the definition that is used, an interview may be a more valid method compared to  
21 survey and questionnaire methodologies. Based on the limitations of parent report, it seems  
22 essential to combine several methods and adapt some of the definitions in order to measure 'true  
23 regression' instead of the normal variation in behavioral changes in children. For example, to validate  
24 the parental history of early development on both the ADI-R and the Diagnostic Interview for Social  
25 and Communication Disorders (DISCO; Wing, Leekam, Libby, Gould, & Larcombe, 2002)  
26 contemporaneous child health records were used by Baird et al. (2008). In the study by Ozonoff et al.

(2005) recall and reliability problems on the EDQ were reduced by (i) limiting the age range of participants to children under 10 years, (ii) suggesting parents to review baby books or calendars prior to completion of the questionnaire and (iii) conducting follow-up calls on missing answers. Another method to enhance the reliability of parent reports is to code data from the ADI-R and/or other interviews and/or questionnaires by independent researchers to establish inter-observer consistency (Wilson et al., 2003). In the study by Goldberg et al. (2003) interrater reliability on the RSF was established by independent recoding of the in-person interviews that had been videotaped. In a study by Davidovitch et al. (2000) the interviewers conducted simulation interviews together with an interrater coding reliability procedure in order to establish reliability between interviewers. In some of the articles using medical records (e.g., Richler et al., 2006) the report of regression was verified by a review of the child's ADI-R protocol including the interviewer's notes and/or a brief follow-up telephone interview with the child's parent. In studies from Luyster et al. (2005) and Richler et al. (2006), long-term reliability of parental reports of regression, based on an initial ADI-R administration and follow-up telephone interview, were reported as being higher than 80%. Only approximately 3% of the children were reclassified after the telephone interview (Luyster et al., 2005; Richler et al., 2006).

### **Retrospective Home-Video Analysis**

Another commonly-used retrospective method to measure characteristics of early development and onset patterns in ASD is observer coded home-video analysis of children who later receive a diagnosis of ASD. These home videos are also often used as a method to validate the parent reports of regression in which the behavior in home videos before and after the age of the lost skills is compared (e.g., Goldberg et al., 2008; Maestro et al., 2006; Ozonoff et al., 2011; Werner & Dawson, 2005). Generally, a series of videos is used to document a decrease of the frequency of key language and socio-communication skills that are typically present very early in life such as gaze, social smiling, response to name, and joint attention (Goldberg et al., 2008; Ozonoff et al., 2011; Werner & Dawson, 2005; Zhang et al., 2018). Some authors use a more standardized scale to measure different

behaviors in home-video's such as the Behavioral Summarized Evaluation scale (BSE; Barthelemy et al., 1990; Maestro et al., 2005; Maestro, Casella, Milone, Muratori, & Palacio-Espasa, 1999). Further, there is a broad variation in the kind of home videos collected. For example, videos have been collected at certain age points, such as first and second birthday parties (Werner & Dawson, 2005) or at 6, 12, 18 and 24 months (Goldberg et al., 2008), throughout the first years of life (e.g., 6 to 24 months (Ozonoff et al., 2011) or from birth until 18 months (Maestro et al., 2006).

Home-videos provide information on the early behaviors of infants often long before the time of clinical diagnosis and can thus corroborate the clinical validity of the phenomenon of regression (for a review on home movie studies in infants with ASD see Saint-Georges et al., 2010; for a review on home movie studies in ASD, Rett syndrome and FXS see Roche et al., 2018). In this regard, the studies of Maestro et al. (2005) and Maestro, Casella, Milone, Muratori and Palacio-Espasa (1999) which included 40 and 26 children respectively, found that in a few cases of ASD, symptoms only started after the first year of life providing evidence for the late-onset or regression type of ASD. In addition to the use of home videos to evaluate the validity of parent reports on onset patterns, these observational data, when collected over different ages, can also be used in a longitudinal, prospective manner to derive different trajectories from the data through statistical modeling approaches. A study by Ozonoff et al. (2011) found three different trajectories (early onset, regression, and plateau) based on discrete behavior measurement from home video segments between 6 and 24 months of age.

Although home-video analysis reduces several of the reporting biases of parent reports, there are still different issues such as the broad variability in the amount, content, representativeness and quality of filming across families which makes it very difficult to analyze these data on characteristics of early development in a standardized and reliable manner (Marschik & Einspieler, 2011; Palomo, Belinchón, & Ozonoff, 2006). A first considerable obstacle is the fact that parents are likely to film their children during special family events (e.g., first and second birthday parties) and turn off the camera when their child is misbehaving or demonstrating behaviors such as repetitive or stereotyped

1 play. Hence, they put less time in recording their child in difficult periods of development, which  
2 makes it challenging to collect videos from children who are showing atypical behaviors or are losing  
3 skills. Compared to parent report, the clinical observations are limited to small fragments of the  
4 child's life and may not represent the typical behavior of the child (Dawson, 2011). Last, collecting  
5 and coding home-videos is a very time-consuming method to gather information on early  
6 development and thus less practical to use in both a clinical and research context (Ozonoff et al.,  
7 2008).

8 Several studies used home-video analyses to validate parent reports on regression (for a  
9 commentary see Marschik, 2014). In a study by Goldberg et al. (2003) parent reports of regression in  
10 language and non-language skills through the ADI-R and supplemental questions on the RSF were  
11 validated by independent observer-coded home-videotapes at 6, 12, 18 and 24 months of almost  
12 30% of the participants. The study by Werner and Dawson (2005) concluded that parent report of  
13 symptom onset was mainly valid, but also demonstrated that although some children were reported  
14 by their parents on the ADI-R to never have shown a regression, they still demonstrated a significant  
15 decrease in their use of social gaze over the 12 to 24 months period on their home videos. Moreover,  
16 Goldberg et al. (2008) reported better concordance between parental report and direct observation  
17 of home videos for onset and loss in expressive language (85%) compared to onset and loss in non-  
18 language domains (49%; e.g., social gaze, joint attention, orienting to name, pointing, showing,  
19 functional and symbolic play). Although there was hardly any agreement between the ADI-R and the  
20 video codes for non-language regression, the agreement between the supplementary interview RSF  
21 and videotape codes was reasonable, indicating that a supplemental interview on non-language  
22 regression may be useful to enhance the reliability of parental report (Goldberg et al., 2008). In the  
23 study by Ozonoff et al. (2011), which focused on the loss of mainly social-communicative variables,  
24 less than half of the onset patterns derived from the ADI-R were supported by trajectories identified  
25 through latent class analysis of the home videos. Overall, it seems more difficult for parents to report  
26 on loss in social skills than on loss of productive language. Further, correspondence between parent

reports and home-videos was also dependent on the level at which the correspondence was calculated (e.g., group level instead of individual level; Werner & Dawson, 2005).

Although over several decades researchers have examined the phenomenon of regression in ASD, there is still no overall consensus on how 'regression' should be defined or operationalized. Findings on regression rates, onset, domains and etiology are inconsistent and sometimes conflicting perhaps owing to such fundamental differences in definitions of regression and other onset patterns, sampling strategies, and methods used. It seems clear that the broad variation in the definition of regression and limitations of both parent reports and home-video analysis mainly lead to an underestimation of the prevalence of regression in ASD. Children who are classified as ASD+REG in some studies would be missed by other studies. Furthermore, most studies on onset patterns in ASD used a dichotomous framework (i.e. regression or no regression) without attention to characteristics of development before regression or the differentiation between plateau and loss of skills.

#### **Review of Retrospective Results on Early Development and Later Outcomes of Regression**

Based on the above described limitations of retrospective methods to classify onset groups in ASD, it has to be mentioned that the reviewed results on early development before and later outcomes after regression should be interpreted with caution. The results need to be confirmed in future studies that implement different strategies to improve the retrospective method and in prospective longitudinal studies.

Although the present study did not intend to conduct a formal systematic review procedure, an overview of the literature selection process is provided to clarify why a particular study was in- or excluded. The literature review was conducted using Web of Science and PubMed (MEDLINE) databases. The search terms were defined through a combination of Medical Subject Headings (MeSH) terms chosen by the first author of the review. Articles in Web of Science were selected by the following search criteria (TS = field tag for topic): ((TS=(Autis\* OR Autism Spectrum Disord\* OR ASD OR 'Autistic Disord\*' OR Pervasive Developmental Disord\* OR PDD OR Asperger\*) AND TS=(regress\* OR

loss\* OR setback)) AND LANGUAGE: (English) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1964-2018). Articles in Pubmed were selected by the following criteria: (((Autis\* OR Autism Spectrum Disord\* OR ASD OR Autistic Disord\* OR Pervasive Developmental Disord\* OR PDD OR Asperger\*)) AND (regress\* OR loss\* OR setback)) AND ("1964"[Date - Publication]: "3000"[Date - Publication])) AND "English"[Language]]. For each database, the search was limited to research studies published in English peer reviewed journals that included data regarding regression in individuals with ASD with regard to the early development before regression or later outcomes after regression. The diagnosis of ASD needed to be based on the DSM-III, DSM-III-R, DSM-IV, DSM-IV-TR or DSM-5 criteria. Also studies with a diagnosis of ASD based on the International Classification of Diseases (ICD) 9<sup>th</sup> and 10<sup>th</sup> Revisions (ICD-9 and ICD-10) were included. Studies using a prospective, longitudinal design to study onset patterns in ASD, reviews, case-studies and studies on etiology of regression were excluded. Although the search initially included articles from 1964 onwards, later on it was decided to exclude studies published before the publication of the DSM-III (1980), which introduced a widely accepted definition of autism. A search through the references of research articles and reviews and an ancestry research resulted in additional citations. After reading the full texts, 7 articles were included for analysis on early development before regression, 19 articles on later outcomes after regression and 19 articles reported results on both topics (for an overview of the selected articles see Table 1 and Table 2).

### **Early Development Before Regression**

In general, there seems to be a broad individual variation in skill attainment and the presence of ASD characteristics prior to the onset of regression. Evidence supports both the presence of a regression pattern with prior (apparently) typical development, and a mixed pattern with early onset of symptoms or developmental delays and regression. However, there is only limited evidence for a specific 'regressive phenotype' of ASD which is characterized by normal pre-loss development (Richler et al., 2006; Werner et al., 2005) and it seems that the emergence of ASD characteristics could be better considered dimensional with different continua based on varying degrees of early



attainment of skills and degrees of loss of skills (cf. supra; Ozonoff et al., 2011; Ozonoff, Heung, et al., 2008; Thurm et al., 2014). Although the traditional definition of regression in ASD assumes a typical development prior to the loss of skills, a sizeable number of studies concluded that a substantial subset (ranging from 41 to 86%) of ASD+REG are reported by their parents to show early delays and atypicalities prior to regression in language, socio-communicative and play development together with problems in regulatory behaviors and the presence of sensory-motor or repetitive behaviors. Hence, typical development seems to be the exception for a sizable number of ASD+REG, and these findings support the existence of a mixed early onset + regression pattern in some children (Ozonoff et al., 2008). In comparison to children with a typical development and children with developmental delays, children with ASD+REG show indeed more impairments in these areas before the age of 24 months (Luyster et al., 2005; Richler et al., 2006). Also home-video study results show that subtle signs of ASD are already present in ASD+REG between 6 and 12 months (Maestro et al., 2006). In contrast, different home-video studies (Maestro et al., 2006; Osterling, Dawson, & Munson, 2002) found that the development of social and communicative abilities seems to be similar between ASD+REG and typically developing children until the age of 12 months, providing some evidence for the 'original' concept of regression. Moreover, some of the home-movie studies found an even better social and communicative development before 12 months in ASD+REG compared to children with typical development (Ozonoff et al., 2011; Werner & Dawson, 2005).

When the development of ASD+REG is compared to ASD-REG or an early onset of symptoms, more typical early social-communicative and language skills and less behavioral atypicalities are found in ASD+REG based on both parent report and home-video studies (Baird et al., 2008; Luyster et al., 2005; Maestro et al., 2006; Osterling et al., 2002; Ozonoff et al., 2005). However, these differences seem to disappear after the age of 24 months (Werner & Dawson, 2005), probably when the regression sets out.

Further, ASD+REG seem to develop their first words in the typical age limits and earlier as compared to ASD-REG. This finding could be related to the definition of regression since in most

studies a certain level of expressive language prior to the skill loss was required (Jones & Campbell, 2010). Furthermore, mixed results are found concerning the development of first word combinations and sentences. Most ASD+REG do not develop this milestone before the regression which starts at an average onset of 21 months and it seems acquired at variable time points in development, as is also seen in typically developing children. With regard to early motor development, although some studies found evidence for earlier development of first steps in ASD+REG (Davidovitch et al., 2000; Kalb et al., 2010), most results suggest an intact motor system. An overview of the different study characteristics and results described in this section can be found in Table 1.

***[Insert Table 1 about here.]***

#### ***Differences in Early Development Between ASD+REG, ASD-REG, and Typical Development (TD).***

A study by Ozonoff et al. (2005), found that 45% of the ASD+REG were reported to show early social and communication delays (e.g., in joint attention, showing and social games) prior to the onset of regression. However, compared to children with ASD and an early onset of symptoms, children with loss of both communication and social skills showed significantly more typical social and communicative behaviors before 18 months of age (Ozonoff et al., 2005). Similarly, in a study by Luyster et al. (2005) in which loss of both language and socio-communicative skills were examined in a large sample of children with ASD, parents of ASD+REG described more typical, early social-communicative development such as the use of more gestures, greater participation in social games and better nonverbal communication and receptive language in their children before the age of 24 months (and thus before the loss) compared to parents of ASD-REG. However, compared to children with a typical development and developmental delays it was found that most children diagnosed with ASD who experienced a regression before 24 months already demonstrated impairments in pre-speech behaviors, games and routines, actions with objects, communicative gestures, and receptive language prior to the loss (Luyster et al., 2005). Results of the study by Richler et al. (2006) which included the same ASD and TD samples as in Luyster et al. (2005) and 7% of the ASD sample of Lord et al. (2004) indicated that before the age of 24 months, ASD+REG had significantly fewer skills in all

1 areas of the CDI comprising pre-linguistic behaviors, actions with objects, games and routines,  
 2 pretending to be a parent, phrase comprehension, early vocabulary, and early communicative  
 3 gestures. However, when parental reports of the early history of ASD+REG were compared to those  
 4 of children with a typical development on an individual level, nearly 30% of the ASD+REG were  
 5 reported to have communication skills in the 'typical range' in the majority of areas on the CDI  
 6 (Richler et al., 2006). Further, also Baird et al. (2008) described that children with ASD within the  
 7 definite language regression group were reported to show less atypicalities in their development  
 8 during the first year of life than the children with ASD without language regression.

9 In a large population-based surveillance study by Wiggins et al. (2009) developmental concerns were  
 10 noted before a loss of skills in 49% of 285 surveillance records with ASD and documented regression  
 11 in social, communication, play or motor areas. The most commonly reported concerns noted prior to  
 12 the loss were motor delays (24%), language delays (16%) and social behavior delays (10%; Wiggins et  
 13 al., 2009). In contrast to prior studies (Baird et al., 2008; Luyster et al., 2005; Ozonoff et al., 2005) a  
 14 higher proportion of ASD+REG (94%) showed general developmental concerns than ASD-REG (73%;  
 15 Wiggins et al., 2009). More specifically, ASD+REG showed significantly more language delays (88% vs.  
 16 62%), social behavior delays (51% vs. 28%) and delays in play development (25% vs. 11%) than ASD-  
 17 REG (Wiggins et al., 2009). However, these concerns were reported before the age of 36 months  
 18 which is later than 12 months (Baird et al., 2008), 18 months (Ozonoff et al., 2005) and 24 months  
 19 (Luyster et al., 2005) and since the average age of regression is 21 months, it may include the  
 20 concerns of parents during the regression process.

21 Further, within ASD+REG, Luyster et al. (2005) and Richler et al. (2006) showed that children with  
 22 regression in other skills than words (such as gestures or pre-speech behaviors) had similar profiles in  
 23 terms of skill mastery and loss in the early years compared to the children with only word loss.  
 24 Based on the previous studies, ASD+REG seem to have widely varying patterns of pre-loss skill  
 25 attainment, however, most studies used the dichotomous regression or no regression grouping  
 26 strategy regardless of the specific types, amounts and timing of pre-loss skills (Thurm et al., 2014).

Therefore, the study by Thurm et al. (2014) quantified if children ‘ever’ initially attained a skill and the age at which the skill was attained or lost in a group of children with autism and other Pervasive Developmental Disorders (PDD-NOS) and control groups of children with developmental delay and typical development. Loss of at least one skill occurred in the majority in the autism/PDD-NOS group (60-63%), but the amount and type of skills lost was variable and attainment and loss could be considered independent of each other since even children with few skills attained were reported to lose skills (Thurm et al., 2014). Further, at 8 months of age, ASD-REG were reported to show significant delays compared to children with developmental delays, whereas ASD+REG were not reported to have significant delays compared to children with developmental delays until after 18 months (Thurm et al., 2014).

#### ***Findings on Early Development from Retrospective Video Analyses***

Based on analysis of home-videos between 6 and 12 months, Maestro et al. (2006) reported some subtle signs of ASD such as higher non-social attention in ASD+REG. However, while infants with an early onset of ASD showed an early deficit in social attention, ASD+REG presented an increase in social attention until 12 months and a decrease after 12 months (Maestro et al., 2006). Further, Osterling, Dawson, and Munson (2002) found that children diagnosed with ASD who were reported by their parents to have experienced a regression in social and communicative abilities, displayed significantly more instances of orienting to name, increased attention to objects held by others and increased looking at people at the age of 12 months as compared to children with early onset of symptoms. By using a stepwise discriminant analysis based on these three specific behaviors, 90% of the children with ASD could be correctly classified as early versus late onset (i.e. regression; Osterling et al., 2002). In contrast with findings from parent report studies (Luyster et al., 2005; Richler et al., 2006) which detected more impairments in ASD+REG compared to typically developing children before the age of 24 months, no differences were found at 12 months of age in several social and communicative behaviors such as gestures, orienting to name, looking at people and looking at objects held/not held by others, repetitive actions and vocalizations (Osterling et al., 2002). Hence, it

seems that one-year-olds with ASD+REG seem to display higher levels of social and language development compared to one-year-olds without regression. Another striking result is that ASD+REG used babbling or words more frequently than typically developing children at the age of 12 months (Werner & Dawson, 2005). Similarly, Ozonoff et al. (2011) found that ASD+REG displayed even higher rates of eye contact, social smiling, and communicative behaviors before their first birthday compared to typically developing children. However, these results are in conflict with a sizeable number of other studies describing the development of many ASD+REG as atypical before its onset. These latter findings could be explained by the fact that the developmental trajectories were derived via a prospective, statistical modeling approach instead of parent report. Later on, at 24 months, Werner and Dawson (2005) did not find differences anymore between infants with an early onset of ASD and infants with ASD and regression in vocalizations, declarative pointing, word use, social gaze, and orienting to name. Both ASD groups showed lower levels of these socio-communicative behaviors compared to typically developing infants (Werner & Dawson, 2005). Longitudinal analyses of the home-movie data of Werner and Dawson (2005) also showed that both children who were classified as ASD+REG or ASD-REG showed a significant decrease in their use of social gaze between 12 and 24 months and failed to make significant gains in their use of canonical or variegated babbling and productive vocabulary.

### ***Findings on Early Language, Motor and Other Developmental Atypicalities***

Kurita (1985) was the first to describe reports of pre-existing atypicalities in development including lack of stranger anxiety, limited social responsiveness, vocabulary of less than 10 words, and/or no two-word combinations in 78% of children with speech loss. With regard to language level prior to speech loss, most children only used single words, three did not yet use meaningful words but gestural expression or imitative behaviors and only three used two- to three-word utterances (Kurita, 1985). In line with these results, several other studies found evidence for early language delays. In a study by Wilson et al. (2003) delayed early language development was reported in half of the children with ASD and language regression or perceived developmental plateau. Similarly,

Goldberg et al. (2003) described that two-thirds of children with loss of language and at least one non-language skill were reported by their parents to show early delays in language acquisition prior to the loss of skills. In a study by Lord et al. (2004) parents reported that loss of words was preceded by a stagnation in vocabulary development and use of expressive language in most of the children. More specifically, each of these children began to say a few words commonly found in the mental lexicon of toddlers, but then failed to progress (i.e. showed a stagnation) before they stopped talking at a mean age of 16 to 17 months (Lord et al., 2004). In addition, only one of the children in their sample had used phrases before the loss occurred (Lord et al., 2004). More recently, a study by Malhi and Singhi (2012) found that prior to language loss, 87% was reported to only use productive speech at the single word level and had vocabularies of less than five words. Only a small proportion (i.e. 28%) of the children with language regression were able to use two to three-word utterances (Malhi & Singhi, 2012).

In line with findings of a more proficient language development in ASD+REG compared to ASD-REG (Baird et al., 2008; Luyster et al., 2005; Ozonoff et al., 2005), Kurita already suggested in 1985 that children with autism and loss of verbal functions developed meaningful words significantly earlier than those without. Overall, children with language regression seem to achieve the milestone of first words in typical age limits since they spoke in single words at a mean age of 11 months (Lord et al., 2004), 12 months (Jones & Campbell, 2010; Meilleur & Fombonne, 2009), 14 months (Christopher et al., 2004) and 16 months (Baird et al., 2008), which was significantly earlier than children with no language regression [19 months (Christopher et al., 2004), 23 months (Jones & Campbell, 2010), 26 months (Baird et al., 2008) and 27 months (Meilleur & Fombonne, 2009)]. Further, in a study by Pickles et al. (2009) the results showed that children diagnosed with ASD and language regression achieved their first words milestone at a markedly younger age (12 to 13 months) than children with ASD without regression as well as children with specific language disorders (24 to 33 months). According to the degree of language regression, in the study by Baird et al. (2008) children with definite language regression used their first words also at significantly younger age (i.e. 16 months)

1 than children with lower level regression (i.e. 47 months). With regard to children with other skill  
2 regression than language regression, Meilleur and Fombonne (2009) found that they displayed a  
3 delay in the attainment of their first words (i.e. 25 months), similar to non-regressive children (i.e. 26  
4 months). Further, the language regression group said their first word at a significantly younger age  
5 (12 months) than the other skill regression group (28 months; Meilleur & Fombonne, 2009). In the  
6 study by Jones and Campbell (2010) children with a reported language regression spoke in single  
7 words at a similar age compared to children with a language plateau onset pattern (i.e. 13 months).  
8 However, in the very large online survey study by Kalb et al. (2010) it was found that at 18 months,  
9 roughly 30% more children with skill loss achieved words before the plateau and no loss and no  
10 plateau groups.

11 Concerning the development of multi-word utterances, mixed findings have been reported. Kalb et  
12 al. (2010) found that phrase speech was achieved over three months later for children with  
13 regression in language, social and motor skills compared to the no loss and no plateau group. In the  
14 studies by Baird et al. (2008) and Meilleur and Fombonne (2009) a similar, delayed pattern of phrase  
15 acquisition was found for both ASD+REG and ASD-REG. In the study by Baird et al. (2008) no  
16 significant differences between the definite language regression (i.e. 50 months) and no regression  
17 (i.e. 44 months) and lower level regression (i.e. 52 months) were found. Likewise, in the study from  
18 Meilleur and Fombonne (2009) similar results in phrase acquisition were found between children  
19 with other skills regression than language (i.e. 35 months) and ASD-REG (i.e. 41 months). However, in  
20 contrast with the study from Baird et al. (2008), the language developmental milestone of first multi-  
21 word utterance was reached within the expected age range by children with language regression (i.e.  
22 30 months) but not by ASD-REG (i.e. 41 months; Meilleur & Fombonne, 2009). Similarly, in a study  
23 from Pickles et al. (2009) a few children (n=5) in whom language loss occurred after acquisition of  
24 phrases, showed an earlier age (23 months; similar to typically developing children) in the  
25 achievement of their first sentences milestone compared to the non-loss groups (42 to 48 months).  
26 With regard to the type of regression, children with severe loss of skills were least likely to have

1 achieved phrase speech between the age of 3 to 17 years, compared to children in the no loss, no  
 2 plateau and mild regression groups (Kalb et al., 2010). Further, children with primarily social losses  
 3 were at less risk to not attain phrase speech compared to those who primarily lost language (Kalb et  
 4 al., 2010).

5 In a home-movie study by Maestro et al. (1999) a delay in the postural maturity and little motor  
 6 initiative together with hyporeactivity to environmental stimulations was observed in three children  
 7 before the loss of contact. In contrast, most later studies which included larger ASD+REG subgroups,  
 8 found typical or near typical development of early motor skills which did not differ from ASD-REG.  
 9 When children diagnosed with autism with and without speech loss were compared, Kurita (1985)  
 10 found that the distributions of ages of attainment of head control, sitting without support, and  
 11 walking did not differ significantly. Similarly, also in a study by Bernabei, Cerquiglini, Cortesi, and  
 12 D'Ardia (2007) no differences between ASD+REG and ASD-REG were found on the ages at which  
 13 motor developmental milestones were mastered. With regard to the specific developmental  
 14 milestone of first steps, in a study by Wilson et al. (2003) 94% of ASD+REG were reported to walk  
 15 before 18 months of age. Further, Jones and Campbell (2010) found no significant difference in the  
 16 age at first steps in ASD+REG (i.e. 14 months) and ASD-REG (i.e. 16 months), findings that are similar  
 17 to the study by Lord et al. (2004). Likewise, in a study by Meilleur and Fombonne (2009) the motor  
 18 developmental milestone of walking was achieved within the expected age range in the language  
 19 regression (12.5 months), other skill regression (13.2 months) and the non-regressive group (14.4  
 20 months). Furthermore, a study by Ozonoff, Young, Goldring, Greiss Hess, et al. (2008) found that  
 21 rates of movement atypicalities around the age of 12 months in children with both ASD+REG and  
 22 ASD-REG were very similar to those of children with typical development. However, ASD+REG and  
 23 children with developmental delay showed significantly later ages of highest maturity for walking and  
 24 ASD+REG showed also a significantly slower rate of development of walking compared to the  
 25 typically developing group (Ozonoff et al., 2008). Based on the finding that the only difference found  
 26 in ASD+REG was in walking, which was the latest maturing motor behavior studied and the only one



of which acquisition overlaps with the age range at which regression typically occurs (i.e. 21 months), the authors suggested that the results for walking may reflect the regression process and that therefore no warning signs of regression can be found in the motor system (Ozonoff et al., 2008). In the study by Kalb et al. (2010) walking without support was reported to occur earlier for the skill loss group, especially the severe group, compared to the plateau and no loss groups. Also in a study by Davidovitch et al. (2000) ASD+REG were reported to walk independently at an earlier age (i.e. 14.4 months) compared to ASD-REG (i.e. 16.7 months), but this difference did not reach significance, probably due to the small sample sizes. When children with early (<24 months) and late (> 24 months) regression were compared, it was found that children with an early regression took their first steps significantly earlier (i.e. 13.2 months) than children with a later regression (i.e. 16.1 months) and children with no regression and onset of symptoms before 24 months (i.e. 17.7 months; Davidovitch et al., 2000).

Similar to the results of Kurita (1985), several studies described also other early developmental atypicalities, next to language delays, prior to regression. In a study by Siperstein and Volkmar (2004) preexisting delays in the attainment of early developmental milestones were reported in over 50% of the cases prior to regression in language, social and/or motor skills. Also a study by Werner et al. (2005) reported that children with a late onset (i.e. emerging ASD symptoms after the age of 12 months) were not necessarily the children who were reported to lose skills. In 41% of ASD+REG, atypicalities in social responsiveness, communication skills and regulatory behavior and the presence of sensory-motor (or repetitive) behaviors were reported at the age of 10 to 12 months, indicating that almost half of ASD+REG were reported to be symptomatic before the occurrence of regression (Werner et al., 2005).

The early development before regression is characterized by a broad individual variation in skill attainment and presence of ASD features. In contrast to the original definition of regression and in support of the existence of a mixed early onset + regression pattern, a substantial subset of ASD+REG

shows early delays and atypicalities in speech language, socio-communicative and play development together with problems in regulatory behaviors and the presence of sensory-motor or repetitive behaviors. There is only limited evidence for a specific regression subtype of ASD characterized by typical development before the loss. An important implication of the presence of severe symptoms early on could be that it can also lead to an underestimation of the prevalence of regression in retrospective studies, since these children have fewer skills to lose which makes it less likely for parents to detect the regression (see also Pickles et al., 2009). Based on home-video studies, subtle signs of ASD could already be present in ASD+REG between 6 and 12 months, however, other studies found that before the age of 12 months the development of social and communicative abilities in ASD+REG can be very similar or even better as compared to typically developing children. At the age of 24 months, more impairments are found in ASD+REG when compared to children with typical development and differences between ASD+REG and ASD-REG seem to disappear.

#### **Duration and Later Outcomes After Regression**

In general, there have been mixed findings on whether ASD+REG have better, similar or worse long-term outcomes than ASD-REG. Although some studies demonstrate more severe impairments in ASD+REG compared to ASD-REG as measured by ASD core characteristics, cognitive functioning, play, imitation and theory of mind skills, language skills, adaptive behaviors and psychiatric and medical comorbidities, other studies reported similar or even better outcomes. An overview of the different study characteristics and results described in this section can be found in Table 2.

***[Insert Table 2 about here.]***

#### ***Duration of Regression and Regaining of Skills***

Although many children (75 to 92%) eventually regain some or all of the skills that were lost, a wide variation in the duration of loss is seen ranging from 4 to 26 months (Goin-Kochel et al., 2014; Goldberg et al., 2003; Lord et al., 2004; Ozonoff et al., 2005). It is important however to mention that some children seem to never regain their lost skills (Lord et al., 2004).

For many of the participants in the studies of Goldberg et al. (2003) and Lord et al. (2004) the duration of time between loss of productive vocabulary and regaining was relatively brief averaging 4 to 5 months with a regaining of skills when they were 3.5 to 5 years of age. More specifically, in the study by Goldberg et al. (2003) 75% of the parents reported at least some improvement in one or more areas of loss with language skills as the most easily regained skills followed by the return of direct gaze, orient to name, and several social interactive behaviors. Further, in a study by Ozonoff et al. (2005) the majority (i.e. 70%) of the participants in a definite regression group lost all communicative and social skills for a period of 6 months or longer. In a study by Goin-Kochel et al. (2014), using a sample of 2105 children from the Simons Simplex Collection (SSC), it was found that 92% regained their language skills after a mean duration of 26.3 months and this was similar between children with different types of losses.

### ***Outcomes in ASD Core Characteristics***

Most studies including preschool children report no differences between ASD+REG and ASD-REG in the development of later core characteristics of ASD. It can be suggested that characteristics of ASD become more evident over time in ASD+REG, however, mixed results are found at later ages.

Several studies found no differences in ASD core characteristics as measured by the ADI-R and the Autism Diagnostic Observation Schedule-2 (ADOS-2; Lord et al., 2012) between different onset groups, including plateau and early onset + regression, in preschool children (ages 3 to 4; Jones & Campbell, 2010; Ozonoff et al., 2011; Rogers, Young, Cook, Giolzetti, & Ozonoff, 2010; Shumway et al., 2011). Later on, at the age of 5 years, Lord et al. (2004) reported a similar total score on the ADOS for ASD+REG and ASD-REG (16.6 vs. 16.5). At a mean age of 8 years, in a study by Siperstein and Volkmar (2004) no significant differences were found between a group of children with clear loss, possible loss, stagnation and no reported loss or stagnation on the Autism Behavior Checklist (ABC; Krug, Arick, & Almond, 1993, 1980).

However, other studies found evidence for more severe ASD core characteristics in ASD+REG. Zachor and Ben-Itzhak (2016) found that ASD+REG at a mean age of 4 years showed higher Autism

Severity Scores (CSS) on the Social Affect scale of the ADOS and all of ADI-R domains compared to ASD-REG, however, effect sizes were rather small. At a mean age of 9 years, Goin-Kochel et al. (2014) found that only children with losses other than language had higher ASD severity, as measured by the CCS from the ADOS, than those with no losses. Further, also several studies which did not use the standardized ADOS or ADI-R reported more severe ASD characteristics in ASD+REG. In the study by Kalb et al. (2010) it was found that ASD-severity, as measured through online parent report on the Social Responsiveness Scale (SRS; Constantino & Gruber, 2005) and the Social Communication Questionnaire (SCQ; Rutter, Bailey, & Lord, 2002) at a mean age of 8 years, was significantly elevated for ASD+REG compared to children with plateau and no loss and no plateau and that those with more severe losses scored higher relative to those who had more moderate or mild losses. Further, children with social and motor skill losses scored higher on the SRS than children with language loss, and motor skill losses were also associated with higher SCQ scores indicating that children with a severe/and or primarily motor regression had a higher degree of ASD symptom severity (Kalb et al., 2010). Baird et al. (2008) found that both a definite language regression group and a lower-level regression group showed more ASD characteristics on the ICD-10 (WHO, 2007). Estabillo et al. (2018) indicated that at a mean age of 8 years, parents of ASD+REG reported greater ASD overall severity, verbal and nonverbal communication and socialization skills and social relationships on the Autism Spectrum Disorders Assessment Battery for children (ASD-Child; Matson & Gonzalez, 2007) as compared to ASD-REG. In the study by Mire et al. (2018) reports of teachers on the SRS reflected more core-ASD characteristics in ASD+REG between 6 and 18 years, but these ratings were still within the mild-to-moderate concern range and small effect sizes were found.

*Evidence for Poorer Social Functioning in Regression.* Between the ages of 3 to 4 years and at 9.6 years it was found that ASD+REG and ASD-REG did not differ in ASD characteristics as measured by the ADOS, however, these children did have higher scores on the parent-reported ADI-R Social Reciprocity domain indicating poorer social functioning (Richler et al., 2006; Werner et al., 2005). On an individual level, it was also found that a greater percentage of ASD+REG were reported by their

1 parents on the ADI-R to be severely socially impaired compared to ASD-REG, but still a significant  
 2 portion of ASD+REG scored in the moderate to low range on this domain (Richler et al., 2006).  
 3 Furthermore, ASD+REG had a significantly higher proportion of children with both low VIQ scores and  
 4 high ADI-R social reciprocity scores, compared to ASD-REG and the relationship between regression  
 5 and impairment remained after controlling for verbal IQ (Richler et al., 2006). In the study by Malhi  
 6 and Singhi (2012) no significant differences between two age and IQ-matched groups of 35 ASD+REG  
 7 and ASD-REG were found on the total Childhood Autism Rating Scale (CARS; Schopler, Reichler, &  
 8 Renner, 1988) score and total number of DSM-IV symptoms, however, ASD+REG had significantly  
 9 more social deficits compared to ASD-REG.

10 *Evidence for More Repetitive and Stereotyped Behaviors in Regression.* In a study by Wilson et al.  
 11 (2003) it was found that around the age of 4 years stereotypies were described in 85% of ASD+REG.  
 12 Further, in a broad age sample of individuals between 20 months and 29 years, Lam, Bodfish, and  
 13 Piven (2008) identified three subtypes of repetitive behavior in ASD (Repetitive Motor Behaviors  
 14 (RMB), Insistence on Sameness (IS) and Circumscribed Interests (CI)) and found that higher scores on  
 15 the RMB factor were associated with a younger age, lower verbal IQ, greater social and  
 16 communication impairments and the presence of regression. Further, children with a mean age of 9  
 17 years and a possible or definite loss of skills, were reported to show significantly higher levels of  
 18 motor stereotypies than ASD-REG (Lam et al., 2008). Meilleur and Fombonne (2009) found that the  
 19 presence of language regression resulted in no differences in ASD symptom scores as measured  
 20 through the ADI-R, however, the presence of regression in other areas (e.g., social, motor, self-help)  
 21 resulted in greater ASD characteristics at a mean age of 6 years, especially for repetitive behaviors. A  
 22 more recent study by Bradley et al. (2016) found that ASD+REG were more likely than ASD-REG to  
 23 engage in stereotyped speech such as echolalia or scripting and to insist on routine and/or sameness.  
 24 Further, they also had higher rates of sensory impairment, including preoccupation with parts of  
 25 objects, visual inspection, preoccupation with movement and atypical responses to sensory stimuli  
 26 but no significant differences were found in the presence of restricted or fixated interests (Bradley et

al., 2016). The differences were still significant after controlling for intellectual disability, however, it is important to mention that since information was collected from records between birth and 8 years of age, it is unclear if these restricted, repetitive, or stereotyped behaviors occurred prior or after the onset of regression (Bradley et al., 2016).

In contrast with the previous findings, in a smaller study by Estabillo et al. (2018) no differences were found in parent-reported repetitive and stereotyped behaviors on the Autism Spectrum Disorders Assessment Battery for children (ASD-Child; Matson & Gonzalez, 2007a, 2007b) of ASD+REG at a mean age of 8 years.

### ***Outcomes in Cognitive Functioning***

Since some studies report no differences between ASD+REG and ASD-REG in cognitive functioning as measured by the MSEL at early ages (3-5.5 years) it is possible that lower levels of cognitive functioning become more clear at later ages in ASD+REG, which is in line with the results on severity of ASD core characteristics after regression. Most studies on cognitive functioning in ASD+REG are based on formal IQ-testing. Although the MSEL is a standardized measurement of early DQ, IQ scores at later ages as measured by the Wechsler tests (e.g., Wechsler, 2003) tend to be more robust. However, it is apparent that there is a lot of variation in the type of methods used to measure later cognitive functioning which may cause mixed results. **Although it could be that regression is a manifestation of an underlying deteriorating change which also affects later cognitive development, it might also be the case that many of the children with regression were those who already had a lower level of cognitive functioning before the onset of the regression compared to children without regression (Kurita, 1985).**

Between the ages of 3 to 4 years, several studies found no differences in cognitive functioning on the standardized MSEL between ASD+REG and ASD-REG (Hansen et al., 2008; Werner et al., 2005). In a study by Ozonoff et al. (2011) no differences in MSEL scores between an early onset, regression and plateau group were found at the mean age of 3 years. Further, also a large multi-site study from Shumway et al. (2011) found no differences in nonverbal and verbal DQ as measured by the MSEL at

1 a similar age of 44 months between early onset, delay + regression, plateau and regression. At the  
2 age of 5.5 years, Giannotti, Cortesi, Cerquiglini, Vagnoni and Valente (2011) indicated that ASD+REG  
3 did not differ in their non-verbal intelligence as measured by the Leiter-R Brief IQ (Roid & Miller,  
4 1997) compared to ASD-REG. Concerning the different types of regression, at a mean age of 6 years,  
5 a study by Goldberg et al. (2003) did not find any differences in IQ scores between children with ASD  
6 and (i) only language regression, (ii) only non-language regression and (iii) a mixed group, however,  
7 some of these groups contained only two individuals.

8 In contrast to these studies, a very large study by Zachor and Ben-Itzhak (2016) found that ASD+REG  
9 at a mean age of 4 years, had lower cognitive and developmental abilities as measured by different  
10 standardized cognitive assessments compared to ASD-REG. The effect size was however rather small.  
11 Bernabei et al. (2007) conducted a longitudinal study with a sample of 40 children with ASD between  
12 2 and 6 years and reported significantly lower mental ages in ASD+REG as compared to ASD-REG. In a  
13 multiplex ASD family study Parr et al. (2011) found that ASD+REG with a mean age of 9 years had  
14 lower verbal and performance IQ, as measured through different standardized instruments, than  
15 their siblings who did not regress. In the study by Goin-Kochel et al. (2014) at a mean age of 9 years it  
16 was found that any degree of language loss was associated with significantly lower cognitive  
17 outcomes (full-scale IQ, non-verbal and verbal IQ) compared to those with no language losses.  
18 Further, only children who used and lost other skills than language for 3 months had lower cognitive  
19 scores than those with no other losses (Goin-Kochel et al., 2014). Overall, the loss groups were  
20 characterized by mean IQ's in the borderline to mildly-impaired range, while mean IQ scores for the  
21 no-loss group were low-average to average and robust effect sizes were reported (Goin-Kochel et al.,  
22 2014). In another large study, Richler et al. (2006) reported significantly lower mean verbal IQ scores  
23 at a mean age of 9.6 years in the ASD+REG compared to the ASD-REG group, however, within  
24 ASD+REG, bimodal scores on verbal IQ were detected. More specifically, one-third of the ASD+REG  
25 showed high verbal IQ performance (VIQ=90) and the other part had very low verbal IQ scores  
26 (VIQ=40), which provides evidence for a possible continuum of outcome severity in ASD+REG rather

than a distinct subgroup with a specific outcome (Richler et al., 2006). Lastly, at a mean age of 10 years, the study by Mire et al. (2018) reported that ASD+REG had significantly lower scores on nonverbal, verbal and full scale IQ and effect sizes were moderate to large.

Most of the studies in which information on cognitive functioning is based on parent or teacher reports, examiner's clinical observation or secondary information such as medical records, found lower levels of cognitive functioning in ASD+REG. Only the study by Kalb et al. (2010) failed to find significant differences in ID at a mean age of 8 years between different groups differentiated according to age of onset, regression severity, or skill loss. At the age of 38 months, Kurita (1985) found that the rate of children with a very low developmental quotient (DQ; i.e. <60) was significantly higher in children diagnosed with autism and speech loss (79%) compared to autistic children without speech loss (59%). At the ages of 4 and 5 years, in a study by Wilson et al. (2003) cognitive skills were estimated to be limited (i.e. below age expectation but not severely impaired) in 73% of the children with language regression, and in the normal range in only 17% of these children. Further, at approximately the age of 6 years, different studies (Christopher et al., 2004; Kobayashi & Murata, 1998; Shinnar et al., 2001) also reported a significantly lower IQ in ASD+REG. In the study by Christopher et al. (2004), 86% of the ASD+REG had a level of cognitive functioning which was defined as borderline or delayed compared to 55% of the ASD-REG. In the multicenter study by Shinnar et al. (2001) cognition was judged by the clinician to be normal in 25%, suspected abnormal in 45% and clearly abnormal in 28% of the ASD+REG. However, when ASD+REG before 3 years of age were compared to ASD+REG at older ages, no significant differences were found (Shinnar et al., 2001). In addition, Bradley et al. (2016) found that ASD+REG were more likely (68.4%) to have comorbid intellectual disability (ID; IQ≤70) before the age of 8 years compared to ASD-REG (50.8%). Wiggins et al. (2009) reviewed records of 285 eight-year old children diagnosed with ASD and found that a larger proportion of ASD+REG (54%) met criteria for ID and were rated by clinicians as being more impaired (41%) than ASD-REG (37% and 17%, respectively). At a mean age of 11 years, Gadow et al. (2017) found that 46% of the ASD+REG had ID, a percentage which was larger than in the ASD-REG group



(19%). Concerning the type of regression, Lance, York, Lee, and Zimmerman (2014) found that ID was seen in 72% of the 4 to 17-year-old children with social regression, 81% of patients with behavioral regression, and 63.4% of patients with language regression.

#### ***Outcomes in Play, Imitation and Theory of Mind Skills***

Only one longitudinal study by Bernabei et al. (2007), in which 40 children with ASD were followed between the ages of 2 and 6 years, examined outcomes in play skills and found that both ASD+REG and ASD-REG significantly improved over time, however, differences in play skills seemed to increase with age and ASD+REG reached poorer play level outcomes at 6 years.

Concerning to imitation and theory of mind skills, three studies were published. In a study by Rogers, Young, Cook, Giolzetti and Ozonoff (2008) it was found that at a mean age of 36 months children diagnosed with ASD (including both ASD+REG and ASD-REG) and children with typical development or developmental delay demonstrated a similar, poorer performance on deferred imitation tasks compared to the immediate imitation tasks. However, the study by Rogers et al. (2010) in which cognitive abilities and ASD severity was similar in both onset groups, revealed that ASD+REG were more severely affected at preschool age, both in terms of imitation performance and in terms of their response to the functional-nonfunctional manipulation. Further, a study by Matthews et al. (2012) concluded that ASD+REG scored higher than the early onset group and lower or about the same as the typically developing group, indicating an overall advantage for ASD+REG over the early onset group across three of four verbal and non-verbal theory of mind tasks (Matthews et al., 2012). These positive results for ASD+REG could be explained either by the 'developmental cascade theory of ASD' (Rogers et al., 2010; see section on "(Early) Predictors of Later Outcomes After Regression"), or the fact that deficits in ASD+REG may be primarily in the language domain whereby better outcomes can only be seen in non-verbal tasks (Matthews et al., 2012).

#### ***Outcomes in Language Skills***

Most studies provide evidence for impaired language outcomes in children with ASD+REG. Only one study by Davidovitch et al. (2000) with a small sample size (n=19) indicated that ASD+REG had a better level of verbal communication at a mean age of 7 years compared to ASD-REG. Further, a study by Pickles et al. (2009) found that in children with ASD who lost language skills before their first phrases, the phrased speech milestone was delayed (i.e. achievement at 52 months) compared to ASD children without regression or language disorders (i.e. achievement between 42 to 48 months). However, at the age of 10 to 14 years, expressive and receptive language skills were similar in ASD+REG and ASD-REG, whereas for the few (n=5) children who experienced language loss after acquiring phrased speech, cognitive performance at later ages was more variable (Pickles et al., 2009).

Although ASD+REG showed greater socio-communication skill mastery at 24 months, at the age of 36 months, ASD-REG were reported to show more socio-communication and language skills compared to those in the loss groups (Luyster et al., 2005). Further, at a mean age of 3.7 years, Hansen et al. (2008) found that ASD+REG demonstrated lower communication and expressive language scores, however, these differences had a small effect size. Later, at the age of 5 years, Kurita (1985) found that the rate of children with meaningful vocabulary was significantly lower in children with autism and speech loss. Wilson et al. (2003) identified 35% of the children to be still nonverbal at the age of 5 years and thus showing persistent language impairments. Similarly, at 6 years of age, Kobayashi and Murata (1998) reported 13.2% of ASD+REG to have 'very good or good' levels of language development compared to 20.8% of ASD-REG. Later on, at an average age of 22 years, 'very good or good' language levels were seen in 31.4% of ASD+REG and 53.6% of ASD-REG (Kobayashi & Murata, 1998). In the study by Shinnar et al. (2001) only 11% of the children with language regression had normal language 46 months after the start of the regression and in 88% the language was found to be impaired, including 33% of the children who were mute, however, at the age of 6 years some improvement in 57% of the children with regression was noted. Bernabei et al. (2007) found in their longitudinal study that although both ASD+REG and ASD-REG significantly

improved between 2 and 6 years of age, differences with regard to receptive and expressive language and communication and request modalities increased with age and ASD+REG reached poorer communication outcomes. In a study by Norrelgen et al. (2015) significantly more (45%) children diagnosed with ASD, who were classified as nonverbal or minimally verbal, had a reported regression compared to children in the phrase speech group (18%). Conversely, also significantly more ASD+REG (49%) were minimally verbal or nonverbal compared to ASD-REG (18%), thus, about half of ASD+REG had no phrase speech between the ages of 4 to 6.5 years (Norrelgen et al., 2015). At a mean age of 11 years, Gadow et al. (2017) found that ASD+REG have significantly more communication deficits, however, effect sizes were moderate.

### ***Outcomes in Adaptive Behavior***

Concerning outcomes in adaptive behavior, inconsistent results were found. In most studies, later adaptive outcomes were measured by a version of the Vineland Adaptive Behavior Scales (VABS; Sparrow, Balla, & Cicchetti, 1984). Kurita (1985) found that children and adolescents with autism and speech loss between the ages of 2 to 14 years showed a lower level of establishment of bladder and bowel control, ability to change clothes and eating without assistance compared to children without speech loss. Likewise, the study by Zachor and Ben-Itzhak (2016) showed that ASD+REG at a mean age of 4 years had lower communication, daily life and socialization skills, but not motor skills, compared to ASD-REG, however, effect sizes were rather small. Further, ASD+REG from a multiplex family with a mean age of 9 years had lower domain scores than their siblings who did not regress (Parr et al., 2011). At the same age, the study by Goin-Kochel et al. (2014) described that children with any degree of language loss scored significantly lower on adaptive-functioning outcomes in communication, socialization and total adaptive functioning compared to those without language loss. With regard to other kind of losses, only children with other losses had lower adaptive scores than those with no other losses, however, again effect sizes were small to moderate (Goin-Kochel et al., 2014).

In contrast, several studies found no significant differences in adaptive functioning as measured by the VABS between ASD+REG and ASD-REG or early onset in preschool children between 3 to 4 years (Hansen et al., 2008; Jones & Campbell, 2010; Werner et al., 2005) or at a mean age of 9.6 years (Richler et al., 2006). Similarly, the study by Shumway et al. (2011) compared an early onset, delay + regression, plateau and regression group at a mean age of 3.6 years and found no differences in communication, socialization and total adaptive functioning. In a study by Siperstein and Volkmar (2004), in which a group of children with clear loss, possible loss, stagnation and no reported loss or stagnation were compared at the age of 8 years, also no significant differences on the adaptive composite score were found. Further, also in some other studies, which used alternative methods to measure adaptive functioning, no differences between ASD+REG and ASD-REG were found at 3.5 (Malhi & Singhi, 2012) and 22 years of age (Kobayashi & Murata, 1998).

### ***Later Psychiatric and Medical Comorbidities***

Several studies using a dimensional symptom scale (e.g., Aberrant Behavior Checklist; ABC; Aman & Singh, 1986) found no or few differences in the severity of psychopathology in ASD+REG compared to ASD-REG (Hansen et al., 2008; Werner et al., 2005) or no correlation between increased behavioral maladjustment and the presence of language regression (Jones & Campbell, 2010). An explanation could be that symptoms of psychopathology such as emotional and behavioral problems in these studies are examined in preschool children under 5 years of age while many psychiatric disorders only start to emerge in late childhood or adolescence (Gadow et al., 2017). Indeed, different studies including samples of older children and adolescents with a reported regression found greater severity of psychiatric symptoms and maladaptive behaviors. Gadow et al. (2017) showed that ASD+REG was related to greater severity of schizophrenia symptoms in individuals with ASD between 6 and 18 years old as reported by parents but not by teachers. ASD+REG were also more impaired by schizophrenia symptoms in social and academic functioning and in children who ever experienced a regression (also after the age of 36 months) higher symptom severity of attention-deficit/hyperactivity disorder, inattention, and generalized anxiety disorder were reported

by parents, however, all effect sizes were moderate (Gadow et al., 2017). In a study by Estabillo et al. (2018), ASD+REG between 2 and 16 years of age were described by their parents to have more internalizing problems, but similar externalizing problems compared to ASD-REG. In a study by Lance, York, Lee and Zimmerman (2014) no significant differences in the occurrence of self-injurious (such as biting or skin picking) or other problem behaviors (such as aggression, disruption or tantrums) between ASD+REG and ASD-REG between 4 and 17 years were found. Wiggins et al. (2009) found that a larger proportion of ASD+REG showed feeding and sleeping problems and a lack of fear or excessive fearfulness at any time during the first 8 years of life than ASD-REG. However, no significant differences were found for mood difficulties, aggressive behaviors, argumentative or oppositional behaviors, hyperactivity or short attention span, self-injurious behaviors, or temper tantrums (Wiggins et al., 2009). In line with these findings, also in the study by Mire et al. (2018) reports of teachers showed no differences on later internalizing and externalizing behavioral problems, even when controlling for cognitive ability in three age groups of children between 6 and 18 years.

Different studies using parent report provided evidence for enhanced sleeping problems in ASD+REG compared to ASD-REG at the age of 5 to 10 years old (Giannotti et al., 2011) and 2 to 17 years old (Ekinci, Arman, Melek, Bez, & Berkem, 2012). The results in the study by Giannotti et al. (2011) were also supported by a standard overnight multichannel polysomnographic (PSG) evaluation which showed that ASD+REG have a more disrupted sleep pattern. Only the study of Hansen et al. (2008) reported no differences in sleep problems between ASD+REG and ASD-REG at an average age of 44 months as measured by parent report (Hansen et al., 2008).

Further, concerning medical disorders no differences between ASD+REG and ASD-REG in gastrointestinal (GI) problems were found through parent report at the age of 44 months (Hansen et al., 2008) and 9 and 14 years (Baird et al., 2008). Although Richler et al. (2006) found higher rates of GI symptoms for three consecutive months at some point in life for ASD+REG with a mean age of 9.6 years, no significant differences between ASD+REG and ASD-REG in rates of GI disorders were found.

Concerning other past or current medical issues (e.g., respiratory, GI, etc.), in a study by Christopher et al. (2004) no significant differences between a group of ASD+REG and ASD-REG 5-year-olds were found.

With regard to the development after regression, ASD+REG seem to develop similarly to ASD-REG or exhibit more problems in their later functioning. A possible explanation for the discrepant findings on outcome could be that the potentially destructive effects of regression are less obvious at earlier ages and become more pronounced over time when children get older and (cognitive) test scores become more stable. Hence, it seems that the age chosen for follow-up assessment is crucial. Studies that consistently found no or few differences across groups (e.g., Kalb et al., 2010; Lord et al., 2004; Parr et al., 2011; Shumway et al., 2011) were those that studied the youngest samples with preschool-aged children (Bernabei et al., 2007; Goin-Kochel et al., 2014; Lord et al., 2004). The results of the longitudinal study by Bernabei et al. (2007) also indicate a positive developmental trend at younger ages, while from 4 years of age onwards, developmental profiles of ASD+REG and ASD-REG began to differ more markedly with ASD+REG appearing to stagnate.

### **(Early) Predictors of Later Outcomes After Regression**

Several studies examined the impact of early ASD characteristics and language level acquired before the start of the regression on developmental outcomes after regression. Based on the 'developmental cascade theory of ASD', ASD+REG who experienced a relatively typical development before 18 to 24 months of age may be protected from early alterations in social processes that cascade into later impairments and thus show better outcomes later in life compared to children with an early onset of ASD symptoms (Rogers et al., 2010). In line with this theory, in the study by Shinnar et al. (2001) the presence of ASD characteristics before regression was associated with an earlier age at regression, longer duration of the nonverbal period, and a worse prognosis for recovery. On the language level, Lord et al. (2004) found that only children who regressed at the level

of non-specific vocalizations showed a lower IQ and more ASD characteristics by the age of 5 years. Children who underwent a regression after having acquired basic linguistic skills (i.e. the use of words and word combinations) had similar outcomes at 5 years of age compared to children with no word loss (Lord et al., 2004). Likewise, in the study by Kalb et al. (2010) children who attained word combinations and had no parental concerns prior to the loss, had less ASD characteristics and cognitive disability later on in life. However, in contrast to this theory, several studies found evidence that earlier development of social and language skills does not provide a long term protective factor in ASD+REG (Kurita, 1985; Lord et al., 2004). In a study by Parr et al (2011) it was suggested that the loss of any level of language is associated with relatively poor developmental progress since both children in the definite language regression group (>5 words in the productive vocabulary before regression) and the lower level language group (<5 words before regression) had more impaired scores on IQ, ASD characteristics, and adaptive behavior measures as compared to ASD-REG. Further, in a study by Baird et al. (2008) the early development score of the DISCO during the first year of life was unrelated to later outcomes after regression.

Other factors that could influence outcomes after regression are the way in which regression was operationalized and onset age of regression. However, until now, mixed results were obtained. With regard to different regression types, Kalb et al. (2010) found that children with more severe losses and/or primarily motor losses later showed more problematic functioning relative to the children who had more moderate or mild losses or who had losses in the language or social domains. These results are in contrast with findings from Parr et al. (2011) where outcomes were not related to duration or type of loss and a study by Hansen et al. (2008) which found no demographic, medical, cognitive, adaptive, or behavioral differences between ASD+REG and ASD-REG using either broad or narrow definitions of regression. Kobayashi and Murata (1998) were the first to demonstrate that language skills and other aspects of later development are unaffected by onset age of regression since analyses with different cut-off points (e.g., before and after 2 years) gave the same results. Also other studies found that age at

regression was not significantly associated with outcome in IQ, adaptive functioning and ASD characteristics (Baird et al., 2008). On the contrary, in the large surveillance study by Wiggins et al. (2009) it was found that children who regressed at/before 24 months showed significantly more general developmental concerns, such as more play delays, but not language or social delays, than children who regressed after 24 months of age. However, there were no significant differences in the presence of cognitive impairment, perceived level of impairment and developmental concerns before the loss of the skills (Wiggins et al., 2009). Further, very few differences between children who regressed at/before 36 months of age and children who regressed after 36 months were found, except for more language delays in children who regressed at/before 36 months (Wiggins et al., 2009). In contrast, Shinnar et al. (2001) reported no significant differences in language function between children with regression before 3 years of age and those with regression at older ages.

**It can be concluded that developmental functioning and attainment immediately prior to regression onset are no salient predictors of later outcomes. Furthermore, mixed results were found regarding the impact of regression domain, onset age and age cut-off on later development.**

### **Clinical Implications of Regression in ASD**

Despite inconsistencies in study results and methodological limitations, the occurrence of a regression or other onset patterns in ASD such as plateau should be monitored in clinical practice. Even though regression is not included in the diagnostic criteria of ASD, tracking a loss of skills in different developmental domains at multiple time points can be critical for early identification of ASD, especially in children who may be at risk (Estabillo et al., 2018). However, it is important to mention that a number of children with ASD show an apparently typical development before the regression as reported by parents. In addition, a similar development between ASD+REG and typically developing children before the age of 12 months was found in home-video studies (e.g., Osterling et al., 2002). Further, there is a wide variation in the onset age of regression. Hence, some



of the children could be ‘missed’ during early screening for ASD characteristics and therefore several screening occasions could be recommended. Routine developmental surveillance results at 18 months showed that 39% of the children with ASD and ID who had passed the routine screening were reported by their parents to lose skills later on, mostly between 18 and 24 months of age (Carlsson et al., 2016).

Since regression has consistently been associated with earlier diagnosis of ASD (Brett, Warnell, McConachie, & Parr, 2016; Mishaal, Ben-Itzhak, & Zachor, 2014; Rosenberg, Landa, Law, Stuart, & Law, 2011; Shattuck et al., 2009) it is seen as an important marker of ASD risk (Shattuck et al., 2009). However, it is important to mention that diagnostic overshadowing of, for example, neurological disorders can cause delayed diagnosis of ASD (e.g., two years) in children who lost previously acquired language skills (Brett et al., 2016).

For now, a standardized interview or questionnaire obtained from parents or caregivers during the intake procedure to outline the developmental trajectory of the child could be used to indicate if regression has occurred. When parents report a regression, especially with recurrent episodes and multiple organ dysfunctions (e.g., in muscles and retina), important underlying pathophysiology like epilepsy and metabolic and genetic causes should first be investigated by a pediatrician or pediatric neurologist (for mitochondrial diseases see Haas, 2010 and Rose et al., 2018). Yet, full evaluations on (neuro)biological causes of regression can be highly invasive (e.g., screening for mitochondrial diseases see also Parikh et al., 2017) and few children are caught in the midst of their regression which makes it very difficult to investigate.

More insight into the characteristics of regression may lead to the development of targeting interventions to limit the loss (Barger et al., 2013; Pearson et al., 2018). For example, if a certain biological susceptibility to ASD and regression could be found, this could make it possible to intervene at a very early point in the development. Moreover, in order to reduce later problems in development, enhanced intervention or a prevention-oriented approach could be provided. However, at the moment there is no specific diagnostic or therapeutic protocol to encounter children

with regression in clinical practice (see Sigafoos et al., 2019 for an evaluation of interventions in Rett syndrome and other developmental disabilities).

Lastly, from a clinical point of view, the experience of a loss of skills in a child could be a very painful, even traumatic event for parents. Often they search for explanations related to both the environment and themselves. Hence, it is very important to provide support for parents and inform professionals who are working with infants and toddlers so that they can be referred to the appropriate services. It would certainly be of interest and clinical value to address the emotional impact of the loss of skills on parents in future research.

### **Proposals for Future Study of Regression in ASD**

Due to the wide variability in definitions of regression, methods, sampling strategies, sample sizes and outcome variables used, we did not deem it feasible to undertake a formal systematic review procedure or include a meta-analysis. However, the present study aimed to provide the first comprehensive overview based on a selection of the most important literature from the past decades. In line with previous reviews (e.g., Barger et al., 2013; Ozonoff, Heung, et al., 2008; Thurm et al., 2018) it can be concluded that research on onset patterns in ASD needs to be more systematic and do a better job of explaining how regression is defined and measured. At the moment, the concept of regression in ASD is poorly defined and we hope that this review will contribute to more uniformity in the conceptualization in the future. To achieve this goal, we believe that a combination of both retrospective and prospective approaches is needed.

### **A Shift Towards Prospective Longitudinal Research on Onset Patterns in ASD**

Recently, there has been a shift towards the use of prospective longitudinal studies of infants at high risk for ASD with an older affected sibling allowing researchers to systematically observe the development before and at the time that symptoms unfold and thus provide important insights on different onset patterns such as regression (for reviews see Bölte et al., 2013, Jones, Gliga, Bedford,

Charman, and Johnson, 2014 and Szatmari et al., 2016). However, there are several arguments why patterns observed in prospective longitudinal studies using high-risk samples may not generalize to ASD in general and thus prevent us from forming firm conclusions about onset patterns in ASD. For example, HR-sibs who go to have a diagnosis of ASD are by definition children from multiplex ASD families and there is considerable evidence that multiplex and simplex ASD are clinically different (Jones et al., 2014). Further, these studies mostly consist of small samples, however, very large sample sizes are required to find a sufficiently large group of infants who ultimately receive a diagnosis of ASD. Since the children in these studies are examined at several specific time points, the loss and regaining of skills could possibly occur between two ages of assessment and could thus be missed by clinical observation (see also qualitative descriptions of developmental patterns by Bryson et al., 2007). Moreover, recent findings on parent and clinician agreement regarding early behavioral signs in 12- and 18 month-old HR-sibs suggest that parents may detect some clinically informative behaviors based on their day-to-day observations more easily than clinicians do during brief clinical assessments (Sacrey et al., 2018). Lastly, the review by Pearson et al. (2018) on prospective studies of regression concluded that there are also some statistical challenges such as only using standardized scores or group data, no differentiation between loss and stagnation of skills, and no use of longitudinal analyses which produce difficulties in distinguishing stagnation or delays from regression and provide no insights into individual variability within groups.

With regard to the development before regression, only three prospective studies were conducted and reported a more typical development between 2 and 6 months prior to a decline (reviewed in Pearson et al., 2018). To date, most prospective studies examined the development up to 36 months of age and it would be valuable in future studies to follow-up the development of children with different types of regression into school age and beyond.

## **Recommendations on Retrospective Research on Onset Patterns in ASD**

Notwithstanding the value of prospective longitudinal research on onset patterns in ASD, parent report through interviews or questionnaires is still the most practical and cost-effective method to collect information on the early development during research studies and the diagnostic process in clinical practice. For example, a longitudinal assessment of social-communicative behavior through coding frequencies per minute would be very time-consuming and expensive and thus hardly feasible (Goin-Kochel et al., 2014). Since there are currently no user-friendly alternative approaches to retrospective parent report, we provide several recommendations to enhance the validity of future retrospective research on onset patterns in ASD.

With regard to the *definition of regression*, we believe it is necessary for all future studies to provide a transparent definition **and/or compare different regression definitions (e.g., language/social regression and mixed regression). Eventually, researchers should aim for clinical consensus criteria to define regression.** It seems clear that onset patterns in ASD may need to be fine-tuned in subcategories or even dimensionalized to achieve informative results (see also Ozonoff et al., 2010).

Based on previous retrospective and prospective studies, research should focus not only on loss of clear language skills but also loss of subtle socio-communication skills. When studies report on the loss of language skills, they need to define the requirements of the language level before the loss since some researchers also include the use of words in a nonfunctional manner such as echolalia (Barbarelli, 2016; Thurm et al., 2014). Next to losses in language and socio-communicative skills it is also important to look at losses that can occur earlier and in less noticeable areas for both parents and professionals such as sensory and motor skills (e.g., over-pruning theory; Thomas et al., 2016), areas which can also be important for a differential diagnosis (e.g., Rett syndrome). Furthermore, although a lot of attention was given to the loss of productive speech, there are almost no reports on the loss of receptive language, an important aspect of the development of language skills and this should be studied in greater detail. In this respect, it could also be important to measure the discrepancy between early receptive and productive lexical abilities (e.g., Hudry et al., 2010) as a

predictor for later speech-language functions (delayed language acquisition, impairment or late-blooming). In addition, vocabulary acquisition traits should be documented to differentiate consistent or transient lexical restrictions (Marschik, Einspieler, Garzarolli, & Prechtel, 2007) and anticipate later linguistic abilities.

To stand back from the arbitrary limits of 24, 30 or 36 months to define regression, researchers can also include both a broad or more inclusive (e.g., a group in which children ‘ever’ experienced a regression) and narrow (e.g., with a specific age limit) operationalization of regression.

Lastly, it seems also important to take into account gender differences in speech-language development and onset patterns (e.g., Eriksson et al., 2012).

Concerning the *sampling methods* it is more desirable to use a large representative sample of the population of children with ASD or population based sampling instead of a clinically or survey ascertained sample (see also Barger et al., 2013). Further, in future studies on the early and later development of regression it is also favored to use different comparison groups such as typically developing children or children with developmental delays (e.g., Thurm et al., 2014) or to include children with other syndromes to conduct cross syndrome comparisons.

With regard to the *methodology on onset patterns in ASD*, researchers should provide substantial information on the method that is used **and/or include comparisons between different regression measurements**. Based on the above described results, it is clear that the ADI-R is used consistently across both retrospective and prospective studies and will continue to be one of the most important sources of information on early development in ASD. When interviews such as the ADI-R are used, researchers should include additional questions (e.g., Thurm et al., 2014) that more carefully explore the loss of subtle social-communication skills such as changes in social engagement, orienting to name, etc. Further, during interviews it can be helpful for parents to illustrate the behaviors that are queried (e.g., joint attention skills) by using videos with examples of this specific behavior or examples of typical and atypical behaviors. Questions on both interviews and questionnaires could be designed in a way that they provide more clear examples of the kind of behaviors that may be

lost. Research studies also have to include rigorous validation of the reported regression through different methods. First, a combination of questionnaires and interviews could be used. Second, observed losses could be confirmed by review of home-videos taken over time. Third, follow-up clinical interviews could be implemented. To reduce recall biases, researchers can ask parents to use records (such as parental diaries) or review home videos before filling out the questionnaire or conducting the interview.

Concerning the *early development before regression* it can be concluded that the main goal of research until now has been examining if development before regression is typical as stated in original definitions of regression. However, more attention on warning signs or possible predictors of loss of skills is needed. In addition, up to now only the early development of gross motor skills has been investigated. In future studies, it could be interesting to focus more on the development of early fine motor and motor anticipation skills or early general movements (for a review on general movements in ASD and Rett syndrome see Einspieler et al., 2014).

With regard to *later outcomes after regression* the use of well-validated, standardized assessments instead of parent reports or information from clinical reports is recommended. Further, a multifaceted assessment of symptomatology by using multiple raters, settings and methods is considered best practices in child-based evaluations (De Los Reyes & Kazdin, 2005). Concerning domains of later development, more attention is needed on characteristics of executive functioning, underlying differences in ToM ability (Matthews et al., 2012) and later motor development. In future research, it may be important to account for possible mediating factors such as early interventions and/or education or comorbidities. Since ID ( $IQ < 70$ ) is commonly associated with regression in ASD, which makes it difficult to measure the true impact of regression on later outcomes, different studies controlled for IQ in their group comparisons (e.g., Bradley et al., 2016; Mire et al., 2018). However, the association of ID and regression supports the possibility that they share common (underlying) factors and statistical control of ID may not be indicated since it may accidentally also control for effects of regression (Bradley et al., 2016; Dennis et al., 2009). It can be recommended to conduct

additional secondary analyses comparing ASD+REG and ASD-REG without ID to examine if correlates of regression were better accounted for by ID (e.g., Bradley et al., 2016).

On a statistical level, in future studies it seems important to report effect sizes when examining clinical significance of group differences, control for chronological age when this variable is significantly different between onset groups (e.g., Davidovitch et al., 2000) and include larger onset groups with sufficient power to detect differences (Bernabei et al., 2007).

#### **Future Studies Combining Categorical and Dimensional Conceptualizations of Regression.**

The correspondence between the findings in retrospective studies on more overt losses described by a subset of parents and prospective findings on early, subtle losses occurring in the majority of children with ASD needs further investigation (see also Pearson et al., 2018). Therefore, in future studies it would be interesting to examine regression both in a dimensional and a categorical way and compare the results (Ozonoff, Heung, et al., 2008; Thurm et al., 2014). Up till now, only one recent prospective longitudinal study (Ozonoff et al., 2018) combined both approaches to study onset patterns in ASD. Information on onset patterns was collected through four measures that systematically varied the informant (examiner vs. parent), decision type (categorical [regression present or absent] vs. dimensional [frequency of social behaviors]), and timing of the assessment (retrospective vs. prospective; Ozonoff et al., 2018). Additionally, in future retrospective studies, prospective information from records of the attainment of milestones at different age-points could be combined and compared with retrospective parent reports. In several countries, well-baby clinics are offering a free surveillance at different important stages in the development up to the age of 36 months during which there is a follow-up of growth, health status and achievement of milestones of the child. Furthermore, it seems that at the moment we are leaving the path from purely describing what we see into a more signal based and machine learning approach of analyzing audio-video data (e.g., Marschik et al., 2017; Pokorny et al., 2017, 2018). These analyses on signal level can be applied in both future retrospective and prospective studies on onset patterns in ASD. Lastly, by combining different conceptualizations of regression in ASD we believe the main challenges will be in the

integration of other onset patterns than early onset and regression (such as a plateau) and the use of advanced statistical techniques.

#### **Conclusion**

Retrospective research has not yet provided clear answers about whether there is a distinct subtype of children with ASD and regression with a particular etiology and developmental course. Further, the original division between early onset and regressive ASD appears to be too rigid since a substantial number of children present with atypicalities in their early development before the onset of clear regression and some children seem to stagnate rather than to lose skills. Mixed findings on the possible causes, early development, and prognosis are generated by the lack of clarity on the definition of regression and the variation in and imprecision of methodologies used to measure regression. The literature is characterized by conflicting results and some argue that the research to date should be considered preliminary (Barger et al., 2013).

Similarly, prospective longitudinal research on onset patterns in ASD has not yet provided clear answers concerning regression as a specific subtype of ASD which raises the question if regression can still be seen as an exception in the development of ASD. Yet, parent reports on the loss of overt language skills seems to be only the tip of the iceberg and some prospective studies have found that most of the children at high risk for ASD who are receiving the diagnosis later on show declines in their social-communicative development. According to these studies, regression could be the norm in the development of children with ASD and should be seen as a process rather than an event.

The present review study aimed to contribute to a more uniform conceptualization of regression in ASD. Both retrospective and prospective research studies on regression in ASD revealed more insight in how regression is characterized across a continuum of ages and skills. In future studies, the combination of a categorical and dimensional approach combined with both parent report and clinical observation in studies using both a prospective and retrospective assessment can provide an interesting new framework to conduct research on onset patterns in ASD and their impact



throughout the life span. Established robust and reliable results can enhance the clinical usefulness of documenting early loss of skills for both early identification and intervention of ASD.

#### Declaration of Interest

*Sofie Boterberg*: no declaration of interest.

*Tony Charman* discloses that in the past 5 years he has served as a consultant to F. Hoffmann-La Roche Ltd. and received royalties from Sage Publications and Guilford Publications.

*Peter B Marschik*: no declaration of interest.

*Sven Bölte* discloses that he has in the last 5 years acted as an author, consultant or lecturer for Shire, Medice, Roche, Eli Lilly, Prima Psychiatry, GLGroup, System Analytic, Ability Partner, Kompetento, Expo Medica, and Prophase. He receives royalties for text books and diagnostic tools from Huber/Hogrefe, Kohlhammer and UTB.

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## Tables

Table 1

Overview of retrospective parent report and video analysis studies on early development before regression in ASD.

Study by	Subjects	Age	Methods	Regression in ASD (ASD+REG): definition, prevalence and mean onset age	Results on early development
<i>Retrospective parent report</i>					
<b>Kurita (1985)</b>	Infantile autism (n=261)	2 to 14 years	Parent reports: own questionnaire + clinical charts from speech pathologists	<ul style="list-style-type: none"> <li>• <b>Definition:</b> total loss of meaningful words, gestural expressions or imitative behaviors for at least 6 months (&lt; age of 30 months)</li> <li>• <b>Prevalence:</b> 37.2% (n=97)</li> <li>• <b>Onset:</b> 18 months</li> </ul>	<ul style="list-style-type: none"> <li>• 78.3% of ASD+REG showed several developmental atypicalities before the onset of regression, including lack of stranger anxiety, limited social responsiveness, vocabulary of less than 10 words, and/or no two-word phrases</li> <li>• ASD+REG developed meaningful words significantly earlier than ASD-REG</li> <li>• The distribution of ages of attainment of head control, sitting without support, and walking did not differ significantly between ASD+REG and ASD-REG</li> </ul>
<b>Davidovitch et al. (2000)</b>	ASD (n=40)	Mean age: 7.08 years	Parent reports: own interview	<ul style="list-style-type: none"> <li>• <b>Definition:</b> loss of verbal and non-verbal communication and social skills; Early ASD+REG ≤ 24 months; Late ASD+REG &gt;24 months</li> <li>• <b>Prevalence:</b> 47.5% (n=19); Early ASD+REG: n=11; Late ASD+REG: n=8</li> <li>• <b>Onset:</b> 24.05 months</li> </ul>	<ul style="list-style-type: none"> <li>• ASD+REG started to walk independently earlier compared to ASD-REG</li> <li>• Early ASD+REG took their first steps significantly earlier than later ASD+REG</li> </ul>

<b>Goldberg et al. (2003)</b>	ASD (n=132)	Mean age: 6 years	Parent reports: interview (ADI-R + RSF) and validation by home-videotapes at 6, 12, 18 and 24 months of 30% of the participants	<ul style="list-style-type: none"> <li>• <b>Definition:</b> Expressive language only regression; Non-language skills only regression; Full regression: loss of language and at least one non-language skills (&lt; age of 36 months)</li> <li>• <b>Prevalence:</b> 33% (n=44)</li> <li>• <b>Onset:</b> 18-21 months</li> </ul>	<ul style="list-style-type: none"> <li>• Two-thirds of ASD+REG already showed delays in their language acquisition prior to the loss of skills</li> </ul>
<b>Wilson et al. (2003)</b>	ASD with language regression or perceived plateau (n=196)	Mean age first visit: 4.2 years  Mean age follow-up: 5.3 years (17% of sample)	Parent reports: own questionnaire	<ul style="list-style-type: none"> <li>• <b>Definition:</b> language regression or plateau: any convincing report of loss of previously acquired language skills and/or losses in social and play skills</li> <li>• <b>Prevalence:</b> 100% (only regression and plateau)</li> <li>• <b>Onset:</b> 21.2 months</li> </ul>	<ul style="list-style-type: none"> <li>• Delayed language development before regression was reported in a sizeable proportion of ASD+REG and only 49% of the parents reported a normal language and behavioral development prior to the loss</li> <li>• Early motor development was defined as normal or near normal in most ASD+REG</li> </ul>
<b>Christopher et al. (2004)</b>	ASD (n=82)	2 to 12 years (mean age: 4.7 years)	Parent reports: own clinical interview + additional information by phone	<ul style="list-style-type: none"> <li>• <b>Definition:</b> regression in language</li> <li>• <b>Prevalence:</b> 37.8% (n=31)</li> <li>• <b>Onset:</b> /</li> </ul>	<ul style="list-style-type: none"> <li>• The age of the first word was significantly younger for ASD+REG compared to ASD-REG</li> </ul>
<b>Lord et al. (2004)</b>	Referral ASD (n=110) TD (n=33) DD (n=21)	2 to 5 years	Parent reports: interview (ADI-R)	<ul style="list-style-type: none"> <li>• <b>Definition:</b> Loss of words (ASD+REG); Fluctuating word loss; Loss of vocalization; No word loss</li> <li>• <b>Prevalence:</b> Loss of words: 25%</li> <li>• <b>Onset:</b> Loss of words: 16 to 17 months</li> </ul>	<ul style="list-style-type: none"> <li>• In most ASD+REG, the loss of words was preceded by a plateau in vocabulary development and use of expressive language</li> <li>• Only one of the ASD+REG had used phrases before the loss</li> </ul>
<b>Siperstein &amp; Volkmar (2004)</b>	AUT (n=237) PDD-NOS + Asperger (PDD; n=199) Mental retardation and/or specific language disorders (DD; n=137)	Mean age: 7.9 years	Parent reports: one question on regression + developmental histories from records routinely completed by parents over a 6-year period	<ul style="list-style-type: none"> <li>• <b>Definition:</b> Clear loss of skills in any domain (language, social, motor, behavioral); Possible loss group</li> <li>• <b>Prevalence:</b> Clear and Possible loss: AUT: 11.8% and PDD: 5.5%</li> <li>• <b>Onset:</b> /</li> </ul>	<ul style="list-style-type: none"> <li>• Only 5 subjects with either AUT, other PDD and DD were reported to demonstrate a normal development before regression</li> <li>• In a group of children with Possible loss parents reported preexisting delays in</li> </ul>



<b>Werner et al. (2005)</b>	ASD (n=64) DD (n=34) TD (n=39)	3 to 4 years (mean age: 3.6 years)	Parent reports: interview (ADI-R + EDI)	<ul style="list-style-type: none"> <li>• <b>Definition:</b> only definite scores on losses in language and non-language skills on ADI-R</li> <li>• <b>Prevalence:</b> 27% (n=17)</li> <li>• <b>Onset:</b> /</li> </ul>	<p>the attainment of early milestones in over 50% of the cases prior to regression</p> <ul style="list-style-type: none"> <li>• Parents reported separately on the age of onset and skill losses in children with ASD: children who were reported to have a late onset (&gt;12 months) of ASD characteristics were not necessarily the children who were reported to lose skills</li> <li>• In 41% of the children with loss of skills on the ADI-R, elevated ASD characteristics were also reported on the EDI at 10 to 12 months</li> <li>• Only 16% was reported as having a course of early normal development before the loss of skills</li> </ul>
<b>Ozonoff et al. (2005)</b>	ASD (n=60)	3 to 9 years	Parent reports: questionnaire (EDQ)	<ul style="list-style-type: none"> <li>• <b>Definition:</b> Definite regression in both communication and social domains for 3 months or longer (&lt; the age of 30 months); Heterogeneous mixed regression in communication, social, motor or adaptive domains + atypicalities prior to onset regression</li> <li>• <b>Prevalence:</b> Definite regression: 38.3% (n=23); Heterogeneous mixed group: 13.3% (n=8)</li> <li>• <b>Onset:</b> 16 months (range 12-18 months) for both Definite and Heterogeneous groups</li> </ul>	<ul style="list-style-type: none"> <li>• Definite regression group: significantly more typical social and communicative behaviors &lt; 18 months of age compared to children in the early onset group</li> <li>• 45% of the 31 ASD+REG were reported by parents to show early social and communication delays prior to the onset of the losses</li> </ul>
<b>Luyster et al. (2005)</b>	ASD (n=351) TD (n=31) DD (n=21)	4 to 15 years	Parent reports: interview (ADI-R) + follow-up telephone interview (ADI-R questions on	<ul style="list-style-type: none"> <li>• <b>Definition:</b> ASD WL: word loss &lt; 36 months; ASD NWL-R: loss of other social-communicative skills</li> </ul>	<ul style="list-style-type: none"> <li>• ASD+REG show already impairments in social-communicative and language skills before the regression when compared to TD and DD</li> </ul>

			regression + questions from the CDI)	<ul style="list-style-type: none"> <li>• <b>Prevalence:</b> ASD WL: 35% (n=125) but over-sampling of children with word regression; ASD NWL-R: 17% (n=38)</li> <li>• <b>Onset:</b> ASD WL: 19 months</li> </ul>	<ul style="list-style-type: none"> <li>• ASD+REG showed more gestures, greater participation in social games and better receptive language before the loss than ASD-REG</li> </ul>
<b>Richler et al. (2006)</b>	ASD (n=351) TD (n=31)  (Same ASD sample as in Luyster et al., 2005 and 7% (n=25) of the ASD sample were part of Lord et al., 2004)	Mean age: 9.6 years	Parent reports: interview (ADI-R) + follow-up telephone interview (ADI-R questions on regression + questions from the CDI)	<ul style="list-style-type: none"> <li>• <b>Definition:</b> ASD+REG = Word loss group with word loss &lt; 36 months + No word loss group in areas other than language such as gestures and pre-speech behaviors</li> <li>• <b>Prevalence:</b> 46.4% (n=163) but over-sampling of children with word regression</li> <li>• <b>Onset:</b> /</li> </ul>	<ul style="list-style-type: none"> <li>• &lt; 24 months ASD+REG had significantly fewer skills in all areas of the CDI (pre-speech behaviors, games and routines, actions with objects, pretending to be a parent, phrase comprehension, early vocabulary, and early communicative gestures) than TD</li> <li>• On an individual level, nearly 30% of ASD+REG were reported to have communication skills in the 'typical range' in the majority of areas on the CDI</li> </ul>
<b>Bernabei et al. (2007)</b>	ASD (n=40)	24 to 51 months (mean age: 35.2 months)	Parent reports: own interview and validation by home-videotapes of 62.5% of the children in the study	<ul style="list-style-type: none"> <li>• <b>Definition:</b> loss of acquired, spontaneously exhibited abilities such as use of words, referential gestures, gaze contact, functional use of objects, irrespective of normal or delayed prior language development for at least 3 months</li> <li>• <b>Prevalence:</b> 45% (n=18)</li> <li>• <b>Onset:</b> 20.6 months</li> </ul>	<ul style="list-style-type: none"> <li>• No differences in motor developmental milestones between ASD+REG and ASD-REG</li> </ul>
<b>Baird et al. (2008)</b>	Broad ASD (n=105) Narrow ASD (n=53) Non-ASD neuro-developmental problems (n=97)	9 to 14 years	Parent reports: interviews (ADI-R + DISCO) + child health records	<ul style="list-style-type: none"> <li>• <b>Definition:</b> Definite language regression; Lower-level language regression (regression in social, play, motor and adaptive skills)</li> <li>• <b>Prevalence:</b> Definite language regression in narrow ASD: 30.2% and in broader</li> </ul>	<ul style="list-style-type: none"> <li>• Age of first words in the Definite language regression group is significantly younger than the ASD-REG</li> <li>• No significant difference between the Definite language regression group and ASD+REG in age of phrase speech</li> </ul>

				<p>ASD: 8%; Lower-level language regression in narrow ASD: 8.4% and in broader ASD: 2.6%</p> <ul style="list-style-type: none"> <li>• <b>Onset:</b> 25 months</li> <li>• <b>Definition:</b> ADI-R: Language regression; Other skill regression Any skill regression</li> <li>• <b>Prevalence:</b> 22% (n=30)</li> <li>• <b>Onset:</b> 27.8 months</li> </ul>	<ul style="list-style-type: none"> <li>• The Definite language regression group had lower DISCO total scores (indicating less abnormality) than the ASD-REG</li> </ul>
<b>Meilleur &amp; Fombonne (2009)</b>	ASD (n=135; AUT: n=80; PDD-NOS: n=44; Asperger: n=11)	1.6 to 22.3 years (mean age: 6.3 years)	Parent reports: interview (ADI-R)		<ul style="list-style-type: none"> <li>• Parents and interviewers consistently reported developmental atypicalities prior to the loss</li> <li>• The language developmental milestones of first word and first phrase were reached within normal age limits by the Language regression group but not by ASD-REG</li> <li>• Children with Other skill regression displayed a pattern of language development similar to that of ASD-REG, presenting with a delayed age of first word and of first phrase</li> <li>• The Language regression group said their first word and first phrase at a significantly younger age than the Other skill regression group</li> <li>• The motor developmental milestone of walking was achieved within the normal age limit in the Language regression, Other skill regression and ASD-REG groups</li> </ul>
<b>Wiggins et al. (2009)</b>	ASD (n=285)	Records between 0 and 8 years; all children are 8 years old at the moment of the research	Record-review surveillance data: educational and clinical records	<ul style="list-style-type: none"> <li>• <b>Definition:</b> documented loss of previously acquired skills in social, communication, play, or motor areas</li> <li>• <b>Prevalence:</b> 17% (n=49)</li> <li>• <b>Onset:</b> 28.2 months</li> </ul>	<ul style="list-style-type: none"> <li>• Developmental concerns (e.g., motor, language and social delays) were noted before a loss of skills in 49% of the surveillance records of ASD+REG</li> <li>• A higher proportion of ASD+REG showed general developmental concerns <math>\leq</math> 36 months than ASD-REG</li> </ul>

<b>Pickles et al. (2009)</b>	Depending on classification rules: autism (range n=58-153); ASD (range n=30-63); SLI (range n=3-39); Other (range n=2-126)	9 to 14 years	Parent reports: interview (ADI-R)	<ul style="list-style-type: none"> <li>• <b>Definition:</b> only language regression</li> <li>• <b>Prevalence:</b> depending on classification rules: autism: range 16-31%; ASD: 0-14%</li> <li>• <b>Onset:</b> Range of 25.1-28.4 months</li> </ul>	<ul style="list-style-type: none"> <li>• ASD+REG showed significantly more language and social delays than ASD-REG</li> <li>• A higher frequency of children with ASD+REG showed delays in play development &lt; 36 months compared to ASD-REG</li> <li>• ASD+REG achieved their first words milestone at a markedly younger age than ASD-REG or children with language disorders</li> <li>• Few children in which language loss occurred after acquisition of phrases, showed also an earlier age (similar to TD) in the achievement of their first sentences milestone compared to ASD-REG</li> </ul>
<b>Jones &amp; Campbell (2010)</b>	ASD (n=114)	2 to 5 years (mean age: 41.4 months)	Parent reports: interview (ADI-R) + evaluation reports	<ul style="list-style-type: none"> <li>• <b>Definition:</b> normal development indicated by attainment of at least one age-appropriate language milestone and report of complete loss of such skills</li> <li>• <b>Prevalence:</b> 29.8% (n=34)</li> <li>• <b>Onset:</b> 19.5 months</li> </ul>	<ul style="list-style-type: none"> <li>• ASD+REG spoke in single words at a significantly earlier age than ASD-REG and similar to children with a language plateau onset pattern</li> <li>• No differences in general motor development between ASD+REG and ASD-REG</li> </ul>
<b>Kalb et al. (2010)</b>	ASD (n=2720)	3 to 17 years (mean age: 8.1 years)	Parent reports: own questionnaire	<ul style="list-style-type: none"> <li>• <b>Definition:</b> noticeable loss in a previously acquired skill (social, language or motor) &lt; the age of 36 months</li> <li>• <b>Prevalence:</b> 44% (n=1181)</li> <li>• <b>Onset:</b> 19.53 months</li> </ul>	<ul style="list-style-type: none"> <li>• ASD+REG had less delayed early development compared to children with plateau or no loss and no plateau</li> <li>• First steps and words were reported earlier for the ASD+REG compared to the plateau and no loss and no plateau group</li> <li>• Phrase speech was achieved at a later age for the ASD+REG compared to the no loss and no plateau group</li> </ul>

<b>Malhi et al. (2012)</b>	ASD (n=70)	Mean age: 3.57 years	Parent reports: own interview	<ul style="list-style-type: none"> <li>• <b>Definition:</b> regression in language, social or cognitive skills &lt; the age of 36 months</li> <li>• <b>Prevalence:</b> 50% (n=35) but over-sampling of ASD+REG</li> <li>• <b>Onset:</b> 22.43 months</li> </ul>	<ul style="list-style-type: none"> <li>• The occurrence of regression was in most cases associated with a reported delayed development prior to the regression</li> <li>• Prior to language loss, 86.7% used words at the single word level and had vocabularies of less than five words</li> <li>• Only a small proportion (28.1%) of ASD+REG were able to use two to three-word sentences</li> </ul>
<b>Thurm et al. (2014)</b>	AUT (n=125) PDD-NOS (n=42) DD (n=46) TD (n=31)	15 months to 7 years	Parent reports: interview (RVI)	<ul style="list-style-type: none"> <li>• <b>Definition:</b> language, social-communicative and play loss of skills</li> <li>• <b>Prevalence:</b> AUT: 63% (n=79); PDD-NOS: 60% (n=25)</li> <li>• <b>Onset:</b> between 9 to 36 months</li> </ul>	<ul style="list-style-type: none"> <li>• ASD+REG show a wide variation in number and type of skills attained before loss of skills</li> <li>• At 8 months, the AUT no loss group was reported to show significant delays compared to children with DD</li> <li>• The AUT loss group was not reported to have significant delays compared to children with DD until after 18 months</li> </ul>

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#### *Home-video analyses*

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<b>Maestro et al. (1999)</b>	AUT (n=16) PDD-NOS (n=10)	18 months to 6 years	Home-video analysis of 0 to 36 months	<ul style="list-style-type: none"> <li>• <b>Definition:</b> Regressive type: characterized by a 'free period' before the onset of the first signs of ASD; Fluctuating type: mild delays during the first year of life followed by regression</li> <li>• <b>Prevalence:</b> Regressive Type: 42.3% (n=11); Fluctuating Type: 11.5% (n=3)</li> <li>• <b>Onset:</b> 18 months</li> </ul>	<ul style="list-style-type: none"> <li>• ASD+REG showed a delay in the postural maturity and little motor initiative together with hyporeactivity to environmental stimulations before the loss of skills</li> </ul>
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<b>Osterling et al. (2002)</b>	ASD (n=20) TD (n=20) Mental Retardation (MR; n=14)	2.5 to 10 years	Parent reports: own structured, standardized interview and home-video analysis of birthday parties at 12 months	<ul style="list-style-type: none"> <li>• <b>Definition:</b> Late onset ASD: no atypicalities in behavior at 12 months and regression in social and communication skills &gt; 12 months</li> <li>• <b>Prevalence:</b> 35% (n=7)</li> <li>• <b>Onset:</b> between 18 and 24 months</li> </ul>	<ul style="list-style-type: none"> <li>• At 12 months: ASD+REG &gt; ASD-REG: orienting to name, attention to objects held by others and looking at people</li> <li>• At 12 months ASD+REG =TD: gestures, orienting to name, looking at people and looking at objects held/not held by others, repetitive actions and vocalizations</li> </ul>
<b>Werner &amp; Dawson (2005)</b>	ASD (n=36) TD (n=20)	12 months and 24 months	Parent reports (ADI-R) and home-video analysis of 12 and 24 months	<ul style="list-style-type: none"> <li>• <b>Definition:</b> loss of social and/or communication skills &lt; 36 months</li> <li>• <b>Prevalence:</b> 41.7% (n=15)</li> <li>• <b>Onset:</b> /</li> </ul>	<ul style="list-style-type: none"> <li>• At 12 months: ASD+REG =TD: joint attention skills, ASD+REG &gt; TD: complex babbling and words</li> <li>• At 24 months ASD+REG = ASD-REG (&lt; TD): word use, vocalizations, declarative pointing, social gaze and orienting to name</li> </ul>
<b>Maestro et al. (2006)</b>	ASD (n=30) TD (n=15)	0 to 18 months	Parent reports (Behavioral Summarized Evaluation Scale) and home-video analysis of birth to 18 months	<ul style="list-style-type: none"> <li>• <b>Definition:</b> loss of skills &lt; 36 months</li> <li>• <b>Prevalence:</b> 50% (n=15) but over-recruitment of ASD+REG</li> <li>• <b>Onset:</b> /</li> </ul>	<ul style="list-style-type: none"> <li>• Before 12 months: ASD+REG show a decrease of social attention and increase of non-social attention</li> <li>• At 12 months: in ASD+REG social and non-social attention grow up</li> </ul>
<b>Ozonoff et al. (2008)</b>	ASD (n=54) TD (n=24) DD (n=25)	ASD: 26-61 months DD: 24-56 months TD: 16-42 months	Parent reports (ADI-R) and home-video analysis of 12 months	<ul style="list-style-type: none"> <li>• <b>Definition:</b> language and social interest and engagement &lt; 36 months</li> <li>• <b>Prevalence:</b> 52% (n=28) but over-recruitment of regression</li> <li>• <b>Onset:</b> /</li> </ul>	<ul style="list-style-type: none"> <li>• ASD+REG = ASD-REG = TD: rates of movement atypicalities, acquisition of early motor behaviors or movement atypicalities prior to regression</li> <li>• ASD+REG and DD showed significantly later ages of highest maturity for walking and ASD+REG showed also a significantly slower rate of development of walking compared to TD</li> </ul>
<b>Ozonoff et al. (2011)</b>	ASD (n=52) TD (n=23)	6 to 24 months	Parent reports (ADI-R) and home-video analysis of 6 through 24 months + longitudinal statistical	<ul style="list-style-type: none"> <li>• <b>Definition:</b> regression in language and social-communicative skills &lt; 36 months</li> <li>• <b>Prevalence:</b> 38.5% (n=20)</li> <li>• <b>Onset:</b> /</li> </ul>	<ul style="list-style-type: none"> <li>• Before 12 months: ASD-R &gt; TD: eye contact, social smiling, and communicative behaviors</li> </ul>

modeling of home-  
video analyses

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1 *Note.* ASD= Autism Spectrum Disorder; ASD+REG= Children with ASD and a reported regression; ASD-REG= Children with ASD without a reported regression;  
2 ADI-R= Autism Diagnostic Interview-Revised (Rutter et al., 2008); RSF= Regression Supplement Form (Goldberg et al., 2003); TD= Typically developing  
3 children; DD= children with a developmental delay; AUT= autism as defined in the DSM-IV-TR; PDD-NOS= Pervasive Developmental Disorder – Not  
4 Otherwise Specified; PDD= Pervasive developmental disorders; EDI= Early Development Inventory (Werner & Dawson, 2005; Werner, Dawson, Munson, &  
5 Osterling, 2005); EDQ= Early Development Questionnaire (Ozonoff et al., 2005); RVI = Regression Validation Interview (Lord et al., 2004); CDI=  
6 Communicative Development Inventory (Fenson, 1989); DISCO= Diagnostic Interview for Social and Communication Disorders (Wing, Leekam, Libby, Gould,  
7 & Larcombe, 2002); SLI= Specific Language Impairment

**Table 2**

Overview of retrospective parent report and video analysis studies on later outcomes after regression in ASD.

Study by	Subjects	Age	Methods regression	Methods outcome(s)	Regression in ASD (ASD+REG): definition, prevalence and mean onset age	Results on later outcomes
<b>Kurita (1985)</b>	Infantile autism (n=261)	2 to 14 years	Parent reports: own questionnaire + clinical charts from speech pathologists	Intelligence and other information: parents reports and clinical charts; Adaptive behavior: Japanese version of Vineland Social Maturity Scale	<ul style="list-style-type: none"> <li>• <b>Definition:</b> total loss of meaningful words, gestural expressions or imitative behaviors for at least 6 months (&lt; age of 30 months)</li> <li>• <b>Prevalence:</b> 37.2% (n=97)</li> <li>• <b>Onset:</b> 18 months</li> </ul>	<ul style="list-style-type: none"> <li>• ASD+REG &gt; ASD-REG: rates of very low developmental quotient (DQ&lt;60)</li> <li>• At 5 years: ASD+REG &lt; ASD-REG: rates of meaningful vocabulary</li> <li>• ASD+REG = ASD-REG: number of children in nursery, kindergarten, grade school, and facilities for intellectual disabled children</li> <li>• ASD+REG &lt; ASD-REG: level of establishment of bladder and bowel control, and of eating without assistance; however, the rate of the ability to change clothes in ASD+REG was only significantly lower in boys</li> </ul>
<b>Kobayashi &amp; Murata (1998)</b>	ASD (n=179)	18 to 33.2 years (mean age: 21.9 years)	Parent reports: interview + clinical records	Intelligence at 6 years: Binet or Wechsler intelligence tests or overall clinical evaluation; Language and adaptive functioning: clinical evaluation	<ul style="list-style-type: none"> <li>• <b>Definition:</b> loss of words + loss of interest in the outer world, despite having undergone normal development before onset</li> <li>• <b>Prevalence:</b> 29.6% (n=53)</li> <li>• <b>Onset:</b> /</li> </ul>	<ul style="list-style-type: none"> <li>• At 6 years: ASD+REG &lt; ASD-REG: IQ; ASD+REG &lt; ASD-REG: level of language development</li> <li>• At 22 years: 'very good or good' language levels were seen in 31.4% of the adults with ASD+REG and 53.6% of the ASD-REG; ASD+REG = ASD-REG: adaptive outcomes</li> </ul>



<b>Davidovitch et al. (2000)</b>	ASD (n=40)	Mean age: 7.08 years	Parent reports: own interview	Parent reports: own interview on verbal abilities + clinical records	<ul style="list-style-type: none"> <li>• <b>Definition:</b> loss of verbal and non-verbal communication and social skills; Early ASD+REG <math>\leq</math> 24 months; Late ASD+REG <math>&gt;</math>24 months</li> <li>• <b>Prevalence:</b> 47.5% (n=19); Early ASD+REG: n=11; Late ASD+REG: n=8</li> <li>• <b>Onset:</b> 24.05 months</li> </ul>	<ul style="list-style-type: none"> <li>• ASD+REG <math>&gt;</math> ASD-REG: 42% of ASD+REG were reported to use verbal communication compared to 19% of ASD-REG</li> <li>• Early regression = Late regression: level verbal communications</li> </ul>
<b>Shinnar et al. (2001)</b>	ASD (n=177)	Mean age: 5.7 years	Parent reports in clinical records	Clinical records + judgement by clinicians	<ul style="list-style-type: none"> <li>• <b>Definition:</b> loss of previously acquired language skills whether or not prior language development was normal or delayed</li> <li>• <b>Prevalence:</b> 100% (only language regression)</li> <li>• <b>Onset:</b> 22.8 months</li> </ul>	<ul style="list-style-type: none"> <li>• 46 months after start of regression: 11% of ASD+REG have typical language, in 88% language was found to be impaired, including 33% of the children who were mute. However, in 57% of ASD+REG, some improvement was noted; cognition was typical in 25%, 'suspect' in 45% and clearly atypical in 28% of ASD+REG</li> </ul>
<b>Goldberg et al. (2003)</b>	ASD (n=132)	Mean age: 6 years	Parent reports: interview (ADI-R + RSF) and validation by home-videotapes at 6, 12, 18 and 24 months of 30% of the participants	IQ: SB-FE + MSEL	<ul style="list-style-type: none"> <li>• <b>Definition:</b> Expressive language only regression; Non-language skills only regression; Full regression (=mixed group): loss of language and at least one non-language skills (<math>&lt;</math> age of 36 months)</li> <li>• <b>Prevalence:</b> 33% (n=44)</li> <li>• <b>Onset:</b> 18-21 months</li> </ul>	<ul style="list-style-type: none"> <li>• No differences in IQ between children with ASD and (i) only language regression, (ii) only non-language regression and (iii) a mixed group</li> <li>• Duration of time between word loss and regaining: 4-5 months (age: 3.5 to 5 years). In 75% some improvement in language skills, direct gaze, orient to name, and several social interactive behaviors</li> </ul>
<b>Wilson et al. (2003)</b>	ASD with language regression or perceived	Mean age first visit: 4.2 years	Parent reports: own questionnaire	Cognitive skills: only in some children formal IQ testing, in most children parent report +	<ul style="list-style-type: none"> <li>• <b>Definition:</b> language regression or plateau: any convincing report of loss of previously acquired language</li> </ul>	<ul style="list-style-type: none"> <li>• In 17% ASD+REG: typical cognitive skills; in 73% ASD+REG: limited cognitive skills; in 85% ASD+REG: stereotypies; in 58% ASD+REG: hypotonia; 35% of ASD+REG were still nonverbal at the age of 5 years</li> </ul>

	plateau (n=196)	Mean age follow-up: 5.3 years (only 17% of the sample)		clinical observation; Language skills: clinical observation and own standards	skills and/or losses in social and play skills • <b>Prevalence:</b> 100% (only regression and plateau) • <b>Onset:</b> 21.2 months	and thus showing persistent language impairments
<b>Christopher et al. (2004)</b>	ASD (n=82)	2 to 12 years (mean age: 4.7 years)	Parent reports: own clinical interview + additional information by phone	Parent interview with questions on cognitive functioning and other medical problems	• <b>Definition:</b> regression in language • <b>Prevalence:</b> 37.8% (n=31) • <b>Onset:</b> /	• ASD+REG: significant lower level of cognitive functioning, 86% had a 'borderline' or delayed cognitive functioning compared to 55% of ASD-REG • ASD+REG = ASD-REG: number of past or current medical issues (e.g., respiratory, GI, cardiac etc.)
<b>Lord et al. (2004)</b>	Refferal ASD (n=110) TD (n=33) DD (n=21)	2 to 5 years	Parent reports: interview (ADI-R)	IQ: MSEL + DAS; ASD characteristics: (PL-) ADOS	• <b>Definition:</b> Loss of words (ASD+REG); Fluctuating word loss; Loss of vocalization; No word loss • <b>Prevalence:</b> Loss of words: 25% • <b>Onset:</b> Loss of words: 16 to 17 months	• At 5 years: ASD+REG was only associated with lower IQ and more ASD characteristics in children who regressed at the language level of non-specific vocalizations. Children who developed words and phrases before word loss had similar outcomes to ASD-REG • Duration of time between word loss and regaining: 4-5 months for those who regained speech by the age of 5 years
<b>Siperstein &amp; Volkmar (2004)</b>	AUT (n=237) PDD-NOS + Asperger (PDD; n=199) Mental retardation and/or specific	Mean age: 7.9 years	Parent reports: one question on regression + developmental histories from records routinely completed by	ASD characteristics: ABC; Adaptive functioning: VABS	• <b>Definition:</b> Clear loss of skills in any domain (language, social, motor, behavioral); Possible loss group • <b>Prevalence:</b> Clear and Possible loss: AUT: 11.8% and PDD: 5.5%	• Clear loss = Possible loss = Stagnation and no reported loss: adaptive functioning and ASD characteristics

	language disorders (DD; n=137)		parents over a 6-year period		<ul style="list-style-type: none"> <li>• <b>Onset:</b> /</li> </ul>	
<b>Werner et al. (2005)</b>	ASD (n=64) DD (n=34) TD (n=39)	3 to 4 years (mean age: 3.6 years)	Parent reports: interview (ADI-R + EDI)	Verbal and nonverbal IQ: MSEL; ASD characteristics severity: ADOS and ADI-R; Adaptive behavior: VABS; Aberrant behavior: ABC-Aberrant	<ul style="list-style-type: none"> <li>• <b>Definition:</b> only definite scores on losses in language and non-language skills on ADI-R</li> <li>• <b>Prevalence:</b> 27% (n=17)</li> <li>• <b>Onset:</b> /</li> </ul>	<ul style="list-style-type: none"> <li>• ASD+REG = ASD-REG: verbal and nonverbal IQ; developmental and adaptive functioning, ASD characteristics and aberrant behavior</li> <li>• ASD+REG &gt; ASD-REG: scores on the ADI-R Social-Reciprocity domain indicating poorer social functioning</li> </ul>
<b>Luyster et al. (2005)</b>	ASD (n=351) TD (n=31) DD (n=21)	4 to 15 years	Parent reports: interview (ADI-R) + follow-up telephone interview (ADI-R questions on regression + questions from the CDI)	Parent interview with questions derived from the CDI	<ul style="list-style-type: none"> <li>• <b>Definition:</b> ASD WL: word loss &lt; 36 months; ASD NWL-R: loss of other social-communicative skills</li> <li>• <b>Prevalence:</b> ASD WL: 35% (n=125) but over-sampling of children with word regression; ASD NWL-R: 17% (n=38)</li> <li>• <b>Onset:</b> ASD WL: 19 months</li> </ul>	<ul style="list-style-type: none"> <li>• At 36 months: ASD+REG &lt; ASD-REG: social-communication and language skills</li> </ul>
<b>Richler et al. (2006)</b>	ASD (n=351) TD (n=31)  (Same ASD sample as in Luyster et al., 2005 and 7% (n=25) of the ASD sample)	Mean age: 9.6 years	Parent reports: interview (ADI-R) + follow-up telephone interview (ADI-R questions on regression + questions from the CDI)	Verbal and non-verbal IQ scores: DAS + MSEL; ASD characteristics severity: ADI-R and ADOS; Adaptive functioning: VABS	<ul style="list-style-type: none"> <li>• <b>Definition:</b> ASD+REG = Word loss group with word loss &lt; 36 months + No word loss group in areas other than language such as gestures and pre-speech behaviors</li> <li>• <b>Prevalence:</b> 46.4% (n=163) but over-sampling of children with word regression</li> </ul>	<ul style="list-style-type: none"> <li>• ASD+REG &lt; ASD-REG: verbal IQ, however, within ASD+REG bimodal scores on verbal IQ were detected</li> <li>• ASD+REG &gt; ASD-REG: ADI-R social-reciprocity domain scores</li> <li>• ASD+REG = ASD-REG: ADOS scores</li> <li>• ASD+REG &gt; ASD-REG: rates of GI symptoms for 3 consecutive months at some point in</li> </ul>

	were part of Lord et al., 2004)					
<b>Bernabei et al. (2007)</b>	ASD (n=40)	First visit: 24-51 months (mean age: 35.2 months) + at least 3 follow-ups between 2 and 6 years	Parent reports: own interview and validation by home-videotapes of 62.5% of the children in the study	Prospective changes over time in: - Mental age: the GMDS or Wechsler pre-school and primary school scale of intelligence - Receptive and expressive language  Communicative and request modalities and play activities were measured by self-developed rating scales	<ul style="list-style-type: none"> <li>• <b>Onset:</b> /</li> <li>• <b>Definition:</b> loss of acquired, spontaneously exhibited abilities such as use of words, referential gestures, gaze contact, functional use of objects, irrespective of normal or delayed prior language development for at least 3 months</li> <li>• <b>Prevalence:</b> 45% (n=18)</li> <li>• <b>Onset:</b> 20.6 months</li> </ul>	<p>his or her life; ASD+REG = ASD-REG: rates of GI disorders</p> <ul style="list-style-type: none"> <li>• ASD+REG = ASD-REG: adaptive functioning</li> <li>• ASD+REG &lt; ASD-REG: mental ages</li> <li>• Longitudinal results: both ASD+REG and ASD-REG improved over time but differences in receptive and expressive language and communication and request modalities + play between ASD+REG and ASD-REG increase with age and ASD+REG reached poorer communication and play outcomes.</li> </ul> <p>As from 4 years of age, developmental profiles of the two groups seem to more markedly differ and this trend continues up to 6 years</p>
<b>Hansen et al. (2008)</b>	ASD (n=333)	2 to 5 years (mean age: 44 months)	Parent reports: interview (ADI-R)	Cognitive function: MSEL; Adaptive function: VABS; Maladaptive behaviors: ABC-Aberrant; GI symptoms and sleep habits: own questionnaire	<ul style="list-style-type: none"> <li>• <b>Definition:</b> loss of language and other skills (ADI-R)</li> <li>• <b>Prevalence:</b> 41% (n=138)</li> <li>• <b>Onset:</b> /</li> </ul>	<ul style="list-style-type: none"> <li>• ASD+REG &lt; ASD-REG: communication scores on the VABS, expressive language scores on the MSEL</li> <li>• ASD+REG &gt; ASD-REG: lethargy scores on the ABC</li> <li>• ASD+REG = ASD-REG: GI symptoms and sleep habits</li> </ul>
<b>Baird et al. (2008)</b>	Broad ASD (n=105) Narrow ASD (n=53)	9 to 14 years	Parent reports: interviews (ADI-R + DISCO) + child health records	Epilepsy: ADI-R and medical interview; GI symptoms: questionnaire +	<ul style="list-style-type: none"> <li>• <b>Definition:</b> Definite language regression; Lower-level language regression (regression in</li> </ul>	<ul style="list-style-type: none"> <li>• Definite language regression = Lower-level regression: increased ASD characteristics scores</li> </ul>

	Non-ASD neuro-developmental problems (n=97)			blood test coeliac antibodies; IQ: WISC-III-UK + SPM or CPM; Adaptive behavior: VABS; Severity of ASD characteristics: ICD-10 ASD score	social, play, motor and adaptive skills) • <b>Prevalence:</b> Definite language regression in narrow ASD: 30.2% and in broader ASD: 8%; Lower-level language regression in narrow ASD: 8.4% and in broader ASD: 2.6%	• Language regression was not associated with GI problems. ASD+REG < ASD-REG: current GI problems; ASD+REG = ASD-REG : past GI symptoms
<b>Rogers et al. (2008)</b>	ASD (n=36) TD (n=20) DD (n=21)	15 months to 4.9 years (mean age: 3 years)	Parent reports: interview (ADI-R)	Deferred and immediate imitation: six matched tasks (Meltzoff 1988a, 1988b)	• <b>Onset:</b> 25 months • <b>Definition:</b> loss of language and other skills (ADI-R) • <b>Prevalence:</b> 55.5% (n=20) but over-sampling of ASD+REG • <b>Onset:</b> /	• ASD+REG = ASD-REG = TD = DD: poorer performance on deferred imitation tasks than the immediate imitation tasks • ASD+REG = ASD-REG: deferred and immediate imitation skills
<b>Lam et al. (2008)</b>	ASD (n=316)	20 months to 29 years (mean age: 9.02 years)	Parent reports: interview (ADI-R)	ASD repetitive and restrictive behavior items ADI-R: parent report	• <b>Definition:</b> loss of language and other skills (ADI-R) + distinction Definite and Possible regression • <b>Prevalence:</b> 15.1% (n=43); Definite: 7% (n=20); Possible: 8.1% (n=23) • <b>Onset:</b> /	• ASD+REG > ASD-REG: scores on Repetitive Motor Behaviors (RMB) • ASD+REG > ASD-REG: levels of motor stereotypies
<b>Meilleur &amp; Fombonne (2009)</b>	ASD (n=135; AUT: n=80; PDD-NOS: n=44; Asperger: n=11)	1.6 to 22.3 years (mean age: 6.3 years)	Parent reports: interview (ADI-R)	ASD characteristics: parent reports ADI-R	• <b>Definition:</b> ADI-R: Language regression; Other skill regression Any skill regression • <b>Prevalence:</b> 22% (n=30) • <b>Onset:</b> 27.8 months	• Language regression: no differences in ASD characteristics scores compared to ASD-REG • Regression in other areas (e.g., social, motor, self-help): greater ASD characteristics, especially for repetitive behaviors compared to ASD-REG

<b>Wiggins et al. (2009)</b>	ASD (n=285)	Records between 0 and 8 years; all children are 8 years old at the moment of the research	Record-review surveillance data: educational and clinical records	Cognitive impairment (IQ $\leq$ 70): records; Social, communication, behavioral and adaptive functioning: coded from records	<ul style="list-style-type: none"> <li>• <b>Definition:</b> documented loss of previously acquired skills in social, communication, play, or motor areas</li> <li>• <b>Prevalence:</b> 17% (n=49)</li> <li>• <b>Onset:</b> 28.2 months</li> </ul>	<ul style="list-style-type: none"> <li>• ASD+REG &gt; ASD-REG: proportion of children who met criteria for ID (IQ score <math>\leq</math> 70) + were rated by clinicians as being more impaired; proportion feeding and sleeping difficulties and a lack of fear or excessive fearfulness at any time</li> <li>• ASD+REG = ASD-REG: mood difficulties, scattered cognitive skills, aggressive behaviors, argumentative or oppositional behaviors, delayed motor milestones, hyperactivity or short attention span, odd responses to sensory stimuli, self-injurious behaviors, or temper tantrums</li> </ul>
<b>Pickles et al. (2009)</b>	Depending on classification rules: autism (range n=58-153); ASD (range n=30-63); SLI (range n=3-39); Other (range n=2-126)	9 to 14 years	Parent reports: interview (ADI-R)	IQ: WISC-III-UK + RSPM or CPM; ASD characteristics: ADOS and ADI-R; Language skills: receptive, expressive and total language scores (CELF-R)	<ul style="list-style-type: none"> <li>• <b>Definition:</b> only language regression</li> <li>• <b>Prevalence:</b> depending on classification rules: autism: range 16-31%; ASD: 0-14%</li> <li>• <b>Onset:</b> Range 25.1-28.4 months</li> </ul>	<ul style="list-style-type: none"> <li>• ASD+REG = ASD-REG: expressive and receptive language skills</li> </ul>
<b>Jones &amp; Campbell (2010)</b>	ASD (n=114)	2 to 5 years (mean age: 41.4 months)	Parent reports: interview (ADI-R)+ evaluation reports	ASD characteristics: ADOS and ADI-R; Adaptive behavior scores: VABS; Behavioral adjustment: BASC and GAF	<ul style="list-style-type: none"> <li>• <b>Definition:</b> normal development indicated by attainment of at least one age-appropriate language milestone and report of complete loss of such skills</li> <li>• <b>Prevalence:</b> 29.8% (n=34)</li> </ul>	<ul style="list-style-type: none"> <li>• ASD+REG = ASD-REG = plateau: ASD characteristics; adaptive functioning; behavioral maladjustment (internalizing and externalizing problems); clinician impressions of overall functioning</li> <li>• ASD+REG &lt; Language plateau: adaptive social skills</li> </ul>

					<ul style="list-style-type: none"> <li>• <b>Onset:</b> 19.5 months</li> </ul>	
<b>Kalb et al. (2010)</b>	ASD (n=2720)	3 to 17 years (mean age: 8.1 years)	Parent reports: own questionnaire	Intellectual disability IQ<70: parent report; Phrase speech: 1st item SCQ; ASD characteristics: parent report through SRS and SCQ; Educational outcomes: parent report	<ul style="list-style-type: none"> <li>• <b>Definition:</b> noticeable loss in a previously acquired skill (social, language or motor) &lt; the age of 36 months</li> <li>• <b>Prevalence:</b> 44% (n=1181)</li> <li>• <b>Onset:</b> 19.53 months</li> </ul>	<ul style="list-style-type: none"> <li>• ASD+REG = ASD-REG: cognitive disability (IQ&lt;70); Within ASD+REG: no differences in regression severity or type of skill losses</li> <li>• ASD+REG &gt; ASD-REG and plateau: ASD-severity; Within ASD+REG: severe and/or primarily motor skill losses had a higher degree of ASD characteristics severity</li> <li>• Within ASD+REG : children with a severe loss of skills were least likely to have achieved phrase speech; children with primarily social losses were at less risk to not have attained phrase speech compared to those who primarily lost language</li> <li>• ASD+REG + plateau: at increased risk for being placed in a special education setting and have a one-to-one aide than ASD-REG or only plateau</li> </ul>
<b>Rogers et al. (2010)</b>	ASD (n=41) TD (n=22) DD (n=22)	14 months to 5.1 years (mean age: 3.2 years)	Parent reports: interview (ADI-R)	ASD characteristics: ADOS and ADI-R; Object imitation: experimental imitation tasks with a constant motor demands and a functional and non-functional situation	<ul style="list-style-type: none"> <li>• <b>Definition:</b> loss of language and other skills (ADI-R)</li> <li>• <b>Prevalence:</b> 58.5% (n=24) but over-sampling of ASD+REG</li> <li>• <b>Onset:</b> /</li> </ul>	<ul style="list-style-type: none"> <li>• ASD+REG = ASD-REG : ASD characteristics severity</li> <li>• ASD+REG &lt; ASD-REG : early object imitation performance</li> <li>• At the ages of 14 and 30 months: ASD+REG &gt; ASD-REG : item failures in a nonfunctional imitation condition compared to a functional imitation condition</li> </ul>
<b>Ozonoff et al. (2011)</b>	ASD (n=52) TD (n=23)	6 through 24 months	Parent reports: interview (ADI-R) validated by home-video analysis +	Cognitive functioning: MSEL; ASD characteristics: ADOS	<ul style="list-style-type: none"> <li>• <b>Definition:</b> regression in language and social-communicative skills &lt; the age of 36 months</li> </ul>	<ul style="list-style-type: none"> <li>• At 3.25 years: ASD+REG = ASD-REG = plateau: MSEL and ADOS scores</li> </ul>

			longitudinal statistical modeling of home-video analyses		<ul style="list-style-type: none"> <li>• <b>Prevalence:</b> 38.5% (n=20)</li> <li>• <b>Onset:</b> /</li> </ul>	
<b>Giannotti et al. (2011)</b>	ASD (n=40) TD (n=12)	5 to 10 years (mean age: 5.5 years)	Parent reports: interview (ADI-R)	Non-verbal cognitive functioning: LIPS; Sleep: standard overnight multichannel polysomnographic (PSG) evaluation and parent-reported CSHQ + sleep diary	<ul style="list-style-type: none"> <li>• <b>Definition:</b> loss of language and other skills (cf. definition ADI-R)</li> <li>• <b>Prevalence:</b> 45% (n=18)</li> <li>• <b>Onset:</b> 20 months</li> </ul>	<ul style="list-style-type: none"> <li>• ASD+REG = ASD-REG : non-verbal intelligence</li> <li>• ASD+REG &gt; ASD-REG : disrupted sleep patterns at the macrostructural level + NREM alterations at the microstructural level</li> <li>• (ASD+REG &gt; ASD-REG) &gt; TD: bedtime resistance, sleep onset delay, sleep duration and night wakings</li> <li>• ASD+REG = ASD-REG = TD: type of sleep alterations</li> </ul>
<b>Shumway et al. (2011)</b>	ASD (n=272; AUT: n=235; PDD-NOS: n=37)	20 months to 7 years (mean age: 3.6 years)	Parent reports: interview (ADI-R)	Nonverbal and verbal DQ: MSEL; Adaptive functioning: VABS; ASD characteristics: ADOS and ADI-R	<ul style="list-style-type: none"> <li>• <b>Definition:</b> Regression: no early atypicalities, followed by loss; Delay + regression: characteristics by 12 months followed by loss</li> <li>• <b>Prevalence:</b> Regression: 22.4% (n=61); Delay + regression: 26.5% (n=72)</li> <li>• <b>Onset:</b> Regression: 19.44 months; Delay + regression: 17.75 months</li> </ul>	<ul style="list-style-type: none"> <li>• No significant differences between the four onset patterns in nonverbal and verbal DQ, ADOS and ADI-R subdomains and severity scores and socialization, communication and total adaptive functioning</li> </ul>
<b>Parr et al. (2011)</b>	ASD (n=158)	4 to 46 years (mean	Parent reports: interview (ADI-R)	Performance IQ: RPM + MSEL; Verbal IQ: BPVT PPVT; ASD characteristics: ADI-	<ul style="list-style-type: none"> <li>• <b>Definition:</b> Cf. ADI-R + 4 subgroups: definite language regression, lower-level language regression, non-</li> </ul>	<ul style="list-style-type: none"> <li>• ASD+REG &lt; ASD-REG : verbal and performal IQ and adaptive behavior scores</li> </ul>



		age: 8.8 years)		R; Adaptive skills: VABS-II	language regression, language and non-language regression	<ul style="list-style-type: none"> <li>• ASD+REG &gt; ASD-REG : severity of ASD characteristics</li> </ul>
<b>Matthews et al. (2012)</b>	ASD (n=32) TD (n=33)	4 to 16 years (mean age: 8 years)	Parent reports: interview (ADI-R + RSF) + clinical review	ToM: a battery of verbal and non-verbal tasks: change of location, change of contents, verbal appearance-reality and non-verbal appearance-reality	<ul style="list-style-type: none"> <li>• <b>Prevalence:</b> 23.9% (n=105); regression &gt;36M: 3.3% (n=15)</li> <li>• <b>Onset:</b> 21.3 months</li> <li>• <b>Definition:</b> Language regression = acquisition and subsequent loss of words &lt; the age of 24 months</li> <li>• <b>Prevalence:</b> 53.1% (n=17) but over-sampling ASD+REG</li> <li>• <b>Onset:</b> /</li> </ul>	<ul style="list-style-type: none"> <li>• ASD+REG scored higher than ASD-REG and lower or about the same as TD, indicating an overall advantage for ASD+REG over ASD-REG across three of the four ToM tasks</li> </ul>
<b>Malhi et al. (2012)</b>	ASD (n=70)	mean age: 3.57 years	Parent reports: own interview	ASD characteristics: CARS; Motor, social, self-help and communication functioning: DP II; Adaptive behavior: VSMS	<ul style="list-style-type: none"> <li>• <b>Definition:</b> regression in language, social or cognitive skills &lt; the age of 36 months</li> <li>• <b>Prevalence:</b> 50% (n=35) but over-sampling of ASD+REG</li> <li>• <b>Onset:</b> 22.43 months</li> </ul>	<ul style="list-style-type: none"> <li>• ASD+REG = ASD-REG: total CARS score and total number of DSM-IV characteristics; developmental ages of the motor, social, self-help, and communication functioning</li> <li>• ASD+REG &gt; ASD-REG : social deficits</li> </ul>
<b>Ekinici et al. (2012)</b>	ASD (n=57)	2 to 17 years (mean age: 6.9 years)	Parent reports: own interview + medical records, review of videos and photos	Parent reports: interview on medical, developmental and sleep problems	<ul style="list-style-type: none"> <li>• <b>Definition:</b> clear loss in communication, social and interests/behavioral skills &lt;30 the age of months; Type 1: regression after normal social/language development; Type 2: regression as the worsening of previously reported ASD features</li> </ul>	<ul style="list-style-type: none"> <li>• ASD+REG &gt; ASD-REG: sleep problems (mostly difficulty at sleep initiation)</li> <li>• Within ASD+REG: higher frequency of GI complaints/diseases in children with Type 2 than Type 1</li> </ul>

<b>Goin-Kochel et al. (2014)</b>	ASD (n=2105)	4 to 18 years (mean age: 8.9 years)	Parent reports: interview (ADI-R) + own loss supplement	Cognition: DAS-II + MSEL + WISC-IV or WASI; Adaptive functioning: VABS-II; ASD severity: CCS from the ADOS	<ul style="list-style-type: none"> <li>• <b>Prevalence:</b> 56.1% (n=32); Type 1: n=16; Type 2: n=16</li> <li>• <b>Onset:</b> /</li> <li>• <b>Definition:</b> Full losses: ADI-R criteria; Subthreshold losses: includes losses that occurred following 1 month of skill use and lasted for at least 1 month</li> <li>• <b>Prevalence:</b> 36.9% (n=776); Full language loss: 17.5%; Full other losses: 25.4%; Subthreshold language losses: 11.7%; Subthreshold other losses: 1.9%</li> <li>• <b>Onset:</b> Full language loss: 20.2 months; Full other losses: 20.7 months; Subthreshold language losses: 16.9 months; Subthreshold other losses: 24.6 months</li> </ul>	<ul style="list-style-type: none"> <li>• Mean duration of loss = 26.3 months</li> <li>• Children with any degree of language loss scored significantly lower on cognitive outcomes and adaptive functioning than ASD-REG .</li> <li>• Only children with Full other losses had lower cognitive and adaptive scores and higher ASD severity than those with no other losses</li> </ul>
<b>Lance et al. (2014)</b>	ASD (n=125)	4 to 17 years (mean age: 10.9 years)	Medical records: admission note	Self-injurious behaviors and intellectual disability: medical records	<ul style="list-style-type: none"> <li>• <b>Definition:</b> the presence of social, behavioral, or language regression</li> <li>• <b>Prevalence:</b> Language: 33% (n=41); Social: 20% (n=25); Behavioral: 17% (n=21)</li> </ul>	<ul style="list-style-type: none"> <li>• ASD+REG = ASD-REG : self-injurious or other problem behaviors</li> <li>• A co-existing diagnosis of disruptive behavior disorder was seen in 52% of patients with social regression, 57.1% of patients with behavioral regression and 56.1% of patients with language</li> </ul>

					<ul style="list-style-type: none"> <li>• <b>Onset:</b>/</li> </ul>	<p>regression ID was seen in 72% of the patients with social regression, 81% of patients with behavioral regression, and 63.4% of patients with language regression</p> <ul style="list-style-type: none"> <li>• ASD+REG &gt; ASD-REG: rate of minimally verbal or nonverbal children</li> </ul>
<b>Norrelgen et al. (2015)</b>	ASD (n=165)	4 to 6.5 years	Parent reports: own interview + medical records	Classification of speech through parent interview: expressive subdomain of VABS-II	<ul style="list-style-type: none"> <li>• <b>Definition:</b> Loss of words &gt; the age of 15 months. In children younger than 15 months, regression was determined when there was a clear indication of loss of social interest and contact</li> <li>• <b>Prevalence:</b> 24% (n=39)</li> <li>• <b>Onset:</b>/</li> </ul>	
<b>Bradley et al. (2016)</b>	ASD (n=862)	0 to 8 years	Records: parent reports documented in a professional record, historical reference, or professional observation	Records for all children concerning the presence of restricted and repetitive behaviors based on DSM-IV-TR and DSM-5 criteria	<ul style="list-style-type: none"> <li>• <b>Definition:</b> documented loss of previously acquired social, communication and/or play skills</li> <li>• <b>Prevalence:</b> 20.8% (n=179); regression &gt; the age of 36 months: 10.5%</li> <li>• <b>Onset:</b> 24.2 months (range: 9 to 84 months)</li> </ul>	<ul style="list-style-type: none"> <li>• ASD+REG &gt; ASD-REG: comorbid ID; stereotyped speech such as echolalia or scripting and to insist on routine and/or sameness + sensory impairment</li> <li>• ASD+REG = ASD-REG: restricted or fixated interests</li> </ul>
<b>Zachor &amp; Ben-Itzhak (2016)</b>	ASD (n=1224)	15 months to 12 years (mean age: 4.2 years)	Parent reports: interview (ADI-R)	IQ/DQ: MSEL + Bayley + WPPSI (and WISC-IV) + SB-FE + KABC-II; Adaptive skills: VABS; ASD characteristics: ADOS and ADI-R	<ul style="list-style-type: none"> <li>• <b>Definition:</b> definite loss of specified skills in language, social engagement, constructive or imaginary play, or motor skills in the ADI-R</li> <li>• <b>Prevalence:</b> 19% (n=230)</li> <li>• <b>Onset:</b> /</li> </ul>	<ul style="list-style-type: none"> <li>• ASD+REG &lt; ASD-REG: cognitive and developmental abilities (IQ/DQ); VABS scores in communication, daily life and socialization skills</li> <li>• ASD+REG = ASD-REG: scores VABS motor skills</li> <li>• ASD+REG &gt; ASD-REG: ADOS-CSS-SA scores and ADI-R scores in all the examined subdomains</li> </ul>

<b>Gadow et al. (2017)</b>	ASD (n=213)	6 to 18 years (mean age: 10.7 years)	Parent reports: own questionnaire on developmental history: the parent questionnaire	Parents and teachers reported on psychiatric symptoms: DSM-IV-referenced behavior rating scale (CASI-4R); IQ test results were asked to the schools	<ul style="list-style-type: none"> <li>• <b>Definition:</b> Restrictive regression: loss of previously acquired communication and social skills between 18 and 36 months of age; Broadly regression: disregards age of onset and type of skill lost (=full inclusion grouping strategy)</li> <li>• <b>Prevalence:</b> 36% (n=77); regression between 18-36 months: 22.5% (n=48)</li> <li>• <b>Onset:</b> /</li> </ul>	<ul style="list-style-type: none"> <li>• ASD+REG &gt; ASD-REG: criteria for ID (IQ&lt;70); severe ASD characteristics; communication deficits; social deficits; severity of schizophrenia spectrum disorder symptoms; special education services and socially restrictive settings</li> <li>• Perseverative behaviors were not related to ASD+REG</li> <li>• Comparable results were found for children in the inclusive group</li> </ul>
<b>Estabillo et al. (2018)</b>	ASD (n=160)	2 to 16 years (mean age: 8.17 years)	Parent reports: questionnaire ASD-Child (one open-ended question on regression)	Parent reports: ASD-Child + ASD-PBC	<ul style="list-style-type: none"> <li>• <b>Definition:</b> broad definition where both regression after typical development and regression after delays was included</li> <li>• <b>Prevalence:</b> 43.7% (n=70)</li> <li>• <b>Onset:</b> 20.96 months</li> </ul>	<ul style="list-style-type: none"> <li>• ASD+REG &gt; ASD-REG: ASD severity, deficits in nonverbal and verbal communication, deficits in socialization skills; internalizing problems</li> <li>• ASD+REG = ASD-REG: repetitive and stereotyped behaviors; externalizing problems</li> </ul>
<b>Mire et al. (2018)</b>	ASD (n=951)	6 to 18 years (mean age: 9.79 years)	Parent reports: interview (ADI-R)	Current core-ASD characteristics severity: teacher ratings on the SRS and current emotional and behavioral symptoms: ASEBA TRF; Cognitive ability: MSEL + DAS-II + WISC-IV	<ul style="list-style-type: none"> <li>• <b>Definition:</b> language or social skill loss <math>\leq</math> 36 months (ADI-R)</li> <li>• <b>Prevalence:</b> 27.1% (n=258)</li> <li>• <b>Onset:</b> /</li> </ul>	<ul style="list-style-type: none"> <li>• ASD+REG &lt; ASD-REG: scores on nonverbal and verbal and full scale intelligence</li> <li>• ASD+REG = ASD-REG ASD characteristics and ratings of internalizing and externalizing behavior problems</li> </ul>

1 *Note.* ASD= Autism Spectrum Disorder; ASD+REG= Children with ASD and a reported regression; ASD-REG= Children with ASD without a reported regression; ADI-R= Autism  
2 Diagnostic Interview-Revised (Rutter et al., 2008); RSF= Regression Supplement Form (Goldberg et al., 2003); TD= Typically developing children; DD= children with a  
3 developmental delay; AUT= autism as defined in the DSM-IV-TR; PDD-NOS= Pervasive Developmental Disorder – Not Otherwise Specified; PDD= Pervasive developmental  
4 disorders; EDI= Early Development Inventory (Werner & Dawson, 2005; Werner, Dawson, Munson, & Osterling, 2005); EDQ= Early Development Questionnaire (Ozonoff et  
5 al., 2005); CDI= Communicative Development Inventory (Fenson, 1989); DISCO= Diagnostic Interview for Social and Communication Disorders (DISCO; Wing, Leekam,  
6 Libby, Gould, & Larcombe, 2002); SLI= Specific Language Impairment; SB-FE= Stanford-Binet, 4th Edition (Thorndike, Hagen, & Sattler, 1986); MSEL= Mullen Scales of Early  
7 Learning (Mullen, 1995); (PL-)ADOS= (Pre-Linguistic) Autism Diagnostic Observation Scale (DiLavore, Lord, & Rutter, 1995); DAS= Differential Ability Scales (Elliott, 1990);  
8 ABC= Autism Behavior Checklist (Krug & Arick, 1980); VABS= Vineland adaptive behavior scales (Sparrow et al., 1984); ADOS= Autism Diagnostic Observation Schedule  
9 (Lord et al., 2012); ABC-Abberant= Abberant Behavior Checklist (Aman&Singh; 1986) ; GMDS= Griffiths Mental Developmental Scales (Griffiths, 1984); Wechsler pre-school  
10 and primary school scale of intelligence (Wechsler, 1973); WISC-III-UK= Wechsler Intelligence Scale for Children, third edition, revised UK (Wechsler, 1992), RSPM (Raven's  
11 Standard Progressive Matrices) or CPM (Coloured Progressive Matrices (Raven, Court, & Raven, 1990a, 1990b); CELF-R= Clinical Evaluation of Language Fundamentals -  
12 Revised UK (Semel, Wigg, & Secord, 1987); BASC = Behavior Assessment System for Children-Parent Rating Scales, Preschool Form (Reynolds and Kamphaus, 1998); GAF =  
13 Global Assessment of Functioning (GAF; APA 200); SCQ=Social Communication Questionnaire (Rutter, Bailey, & Lord, 2002); SRS = Social Responsiveness Scale (Constantino  
14 & Gruber, 2005); LIPS = Leiter International Performance Scale (Roid & Miller, 1997); CSHQ = Children's Sleep Habits Questionnaire (Owens, Spirito, & McGuinn, 2000);  
15 BPVT = British Picture Vocabulary Test (Dunn, Dunn, Whetton, & Pintilie, 1982); PPVT = Peabody Picture Vocabulary Test (Dunn & Dunn, 1997); ToM = Theory of Mind;  
16 CARS = Childhood Autism Rating Scale (Schopler, Reichler, & Renner, 1988); DP II = Developmental Profile II (Alpern, Boll, & Shearer, 1986); VSMS = Vineland Social  
17 Maturity Scale (Malin, 1971); DAS-II Differential Ability Scales-Second Edition (Elliot, 2007), WISC-IV (Wechsler, 2003); WASI = Wechsler Abbreviated Intelligence Score  
18 (Wechsler, 1999); VABS-II: Vineland Adaptive Behavior Scales – second edition(Sparrow, Cicchetti, & Balla, 2005); CCS: Calibrated Comparison Score (ADOS); Bayley =  
19 Bayley Scales of Infant Development (Bayley, 1993), WPPSI = Wechsler Preschool and Primary Scale of Intelligence (Wechsler, 1989), KABC-II = Kaufman Assessment  
20 Battery for Children-II (Kaufman & Kaufman, 1983) CASI-4R = Child and Adolescent Symptom Inventory-4R (Gadow and Sprafkin, 2005); ASD-Child= the Autism Spectrum  
21 Disorders Assessment Battery for children (Matson & Gonzalez, 2007a, 2007b); TRF = Teacher Rating Form (Achenbach & Rescorla, 2001); GI = gastro-intestinal